The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

THE INTER-RELATIONSHIP BETWEEN CARDIOVASCULAR FUNCTION AND GASTRO-INTESTINAL DISEASE—*Edward Suckle, M. D. and George K. Wharton, M. D.* 261

A CLINICAL STUDY OF THE PATHOGENESIS OF THE DIABETIC SYNDROME—*Bruno W. Volk, M. D. and Sydney S. Lazarus, M. D.* 269

MANAGEMENT OF BOWEL DYSFUNCTIONS IN CHILDREN—*Edward E. P. Seidmon, M. D.* 274

THE EFFECT OF MINERAL OIL ON FOOD UTILIZATION—*Mary F. Paul, Victor R. Ells and Henry E. Paul*....278

LYSOZYME ACTIVITY IN GASTRIC JUICE OF NORMAL ADULTS—*Otto E. Lobstein and Samuel J. Fogelson* 282

THE USE OF ADENOSINE-5-MONO PHOSPHATE IN THE PRURITUS OF OBSTRUCTIVE JAUNDICE—*Louis Pelner, M. D. and Samuel Waldman, M. D.* 283

PERFORATED ESOPHAGEAL ULCER—*J. H. Coffey, M. D. and I. Dravin, M. D.* 285

ABSTRACTS ON NUTRITION, EDITORIAL, BOOK REVIEWS, GENERAL ABSTRACTS OF CURRENT LITERATURE 286-292

Volume 18 September, 1951 Number 9

Copyright 1951, Sandfield Publishing Company

Wyeth®

FOR PROMPT RELIEF OF DIARRHEA

KALPEC combines the benefits of Kaolin, Alumina Gel and Pectin—quickly relieves pain and discomfort . . . soothes and protects irritated intestinal mucosa . . . adsorbs and helps to remove toxins and irritants . . . hastens consolidation of stools.

KALPEC is unusually pleasant-tasting, has a smooth texture . . . invites cooperation of the patient.

DOSAGE IS SELF-LIMITING

Initial dose, 2 tablespoonfuls in about ¼ glass water, then 1 tablespoonful after each bowel movement until diarrhea is checked.

As diarrhea subsides, dosage is reduced—
When diarrhea is stopped, medication is discontinued.

If no satisfactory response is observed within 24 hours, resort to other measures should be considered.

Supplied: Bottles of 12 fl. oz.

KALPEC*

Formerly KAOMAGMA WITH PECTIN

KAOLIN IN ALUMINA GEL WITH PECTIN, WYETH

Wyeth Incorporated, Philadelphia 2, Pa.

*Trade-mark

in peptic ulcer–

NEW CONVENIENT CHLOROPHYLL THERAPY

Chloresium® MUCINOID Tablets · Powder

for rapid relief of symptoms and tissue repair even in intractable cases

All the advantages of CHLORESIUM POWDER* are now available in convenient *tablet* form: same unique combination of healing agent plus antacids in a mucin-like base — same superior clinical results — and in a form that's easy to take.

highly concentrated, purified water-soluble chlorophyll promotes healing of affected areas, duplicating the outstanding results obtained in treatment of external lesions.

specially prepared, mucilaginous okra base clings tenaciously to mucosal walls, protecting against erosion and maintaining the chlorophyll in prolonged contact with the lesion.

prompt, sustained antacid action — without undesirable side effects — provided by magnesium trisilicate and aluminum hydroxide.

packaging: CHLORESIUM MUCINOID is available in bottles of 50 and 200 tablets and in boxes of 25 powders.*

*CHLORESIUM POWDER will continue to be available in boxes of 25 envelopes but will now be sold under the name CHLORESIUM MUCINOID.

RYSTAN COMPANY, INC. Mount Vernon, N. Y.

THE OLDEST PERIODICAL IN ITS SPECIAL FIELD ON THE WESTERN HEMISPHERE

Printing Office:
117 E. Main St.
Berne, Indiana

Business and Editorial Office:
229 West Berry Street
Suite 302-310
Fort Wayne, Indiana

Advertising Office:
Vining & Meyers
35 East Wacker Drive
Chicago 1, Illinois

Annual Subscription Rate $6.00; Two Years, $10.00

Single Copies: Current Year 80c. Back Years $1.00.

Editor: Beaumont S. Cornell
Fort Wayne, Indiana

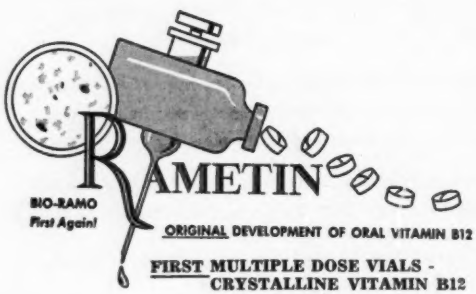
Foreign Subscriptions $7.00; two years $12.00

Regional Editor: Franz J. Lust
17 E. 89th St., New York, N. Y.

EDITORIAL COUNCIL

Clinical Medicine—Diseases of Digestion: Anthony Bassler; John M. Blackford; Leon Bloch; Arthur Leonard Bloomfield; Russel S. Boles; Joseph Edmond Dube; Edward G. Emery, Jr., George B. Eusterman; Harry Gauss; Frank D. Gorham; Russell L. Haden; R. H. M. Hardisty; Charles Lester Hartsock; Blair Holcomb; Harry G. Jacobi; Allen A. Jones; Chester M. Jones; Clement Russell Jones; Noble Wiley Jones; Joseph William Larimore; B. B. Vincent Lyon; Lay Martin; Francis D. Murphy; Moses Paulson; George M. Piersol; Milton M. Portis; Martin Rehfuss; Vernon C. Rowland; Adolph Sachs; Leon Schiff; Daniel M. Silverman; Virgil E. Simpson; Albert M. Snell; Horace W. Soper; Cyrus Cressey Sturgis; Martin G. Verhaus. Gastroscopy, Esophagoscopy: James L. Berland; E. B. Freeman; Chevalier Jackson; Rudolf Schindler; Porter Paisley Vinson. Nutrition: Lloyd Arnold; Clifford Joseph Barborka; Reginald Fitz; Seale Harris; Henry L. John; Howard Frank Root; Nina Simmonds. Surgery of the Lower Colon and Rectum: Louis Arthur Buie; Jerome Morley Lynch; Clement L. Martin; Curtis Rosser; Louis J. Hirschman; Frank C. Yeomans. Bacteriology: Oscar Felsenfeld. Therapeutics: Walter A. Bastedo; Edward S. McCabe. Allergy: Albert H. Rowe; J. Warrick Thomas. Roentgenology: David S. Beilin; Arthur C. Christie; Frederick J. Hodges; William H. Stewart. Parasitology: Robert Hegner; Kenneth Merrill Lynch; Thomas Byrd Magath; Henry Meleney. Experimental Physiology: J. P. Quigley; A. J. Carlson; M. H. F. Friedman; Ira A. Manville; Edward J. Van Liere. Psychiatry and Neurology: William C. Menninger. Abdominal Surgery: Albert A. Berg; Thomas M. Joyce; Rudolph Matas; Edward Wm. Alton Ochsner; James Taft Pilcher; Charles T. Sturgeon.

Published Monthly at 117 East Main St., Berne, Ind.
Correspondence regarding advertising must be addressed to Vining and Meyers, 35 E. Wacker Drive, Chicago. Advertising plates must be sent to M. I. Lehman, 117 E. Main St., Berne, Indiana. Subscriptions, reprint orders, etc., should be addressed to 229 West Berry Street, Suite 302-310 Fort Wayne, Indiana. Manuscripts and books for review must be addressed to Dr. Beaumont S. Cornell, 229 West Berry St., Fort Wayne 2, Ind. Illustrations in excess of six per article are charged at cost to the author. Contents of Journal are fully copyrighted. Copyright 1950, by Sandfield Publishing Co., 229 W. Berry St., Fort Wayne, Ind., in the U. S. A., Vol. 18, No. 9, September, 1951. Entered as second class matter, Sept. 6, 1950, at the Post Office at Berne, Indiana, under the Act of March 3, 1879.



For Economical Vitamin B_{12} Therapy

RAMETIN (crystalline Vitamin B_{12} U.S.P.) has been widely accepted by the medical profession and contains the ONLY vitamin B_{12} official in the U.S.P., XIV.

RAMETIN TABLETS—the **first oral** vitamin B_{21}. Palatable, candy-like in taste, soluble scored tablets. Available in three potencies:

5 microgram tablet-bottle of 25 and 100

10 microgram tablet-bottle of 100.

30 microgram tablet-bottle of 100.

RAMETIN INJECTION—A.M.A. COUNCIL ACCEPTED. the **first multiple dose vial** to be offered to the medical profession and Council Accepted. Available in:

10 cc. vials—10 micrograms and 15 micrograms per cc. of Crystalline Vitamin B_{12} U.S.P., XIV.

LITERATURE ON REQUEST

BIO-RAMO DRUG CO., INC.
Baltimore 1, Md.

FAST RELIEF

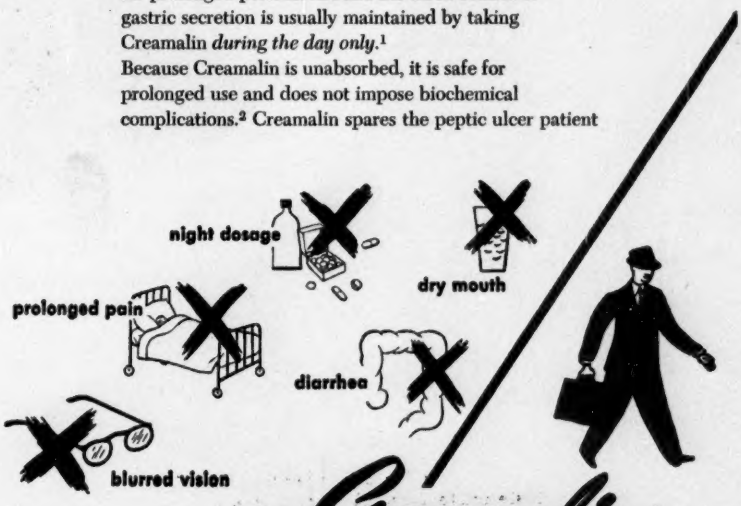
in gastric hyperacidity

When patients with functional gastro-intestinal disorders complain of epigastric distress, heartburn, bloating or dyspepsia, Creamalin gives relief *in minutes.* Creamalin is amorphous acid soluble aluminum hydroxide, the form with fast neutralizing action.

FAST HEALING

in peptic ulcer

Creamalin heals peptic ulcer as quickly as 7 to 10 days. A reactive, demulcent type of gel, it buffers acidity for prolonged periods. Around the clock control of gastric secretion is usually maintained by taking Creamalin *during the day only.*[1]
Because Creamalin is unabsorbed, it is safe for prolonged use and does not impose biochemical complications.[2] Creamalin spares the peptic ulcer patient



Creamalin®

AMORPHOUS ACID SOLUBLE REACTIVE ALUMINUM HYDROXIDE

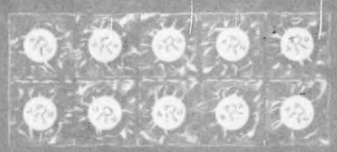
Winthrop-Stearns INC.

NEW YORK 18, N.Y. • WINDSOR, ONT.

1. Breuhaus, H. C.; Akre, O. H., and Everly, J. B.: *Gastroenterology,* 16:172, Sept., 1950.

2. Jordan, Sara M.: *Ann. West. Med. & Surg.,* 4:133, Mar., 1950.

the man who



• Notably pleasing in taste and texture, Rubolate tablets are available sealed in transparent tape and packaged in boxes of 100; or in bulk in bottles of 500.

ACCEPTED BY THE COUNCIL ON PHARMACY AND

A smooth therapeutic course for *develops ULCER*

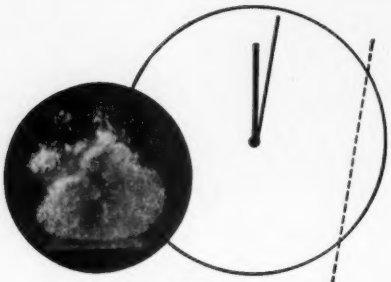
Only by thwarting, somehow, the strong natural forces that normally repair lesions of gastric and duodenal mucosa, has the patient developed ulcer. Only by enlisting and implementing those forces effectively can ulcer be corrected. As an efficient antacid and demulcent, Robalate helps accomplish this with *no acid rebound, no change in acid-base balance,* and *no toxicity*. Robalate provides prompt and prolonged reduction of acidity, a rapid relief from pain. It covers the ulcer and the mucosa with a soft protective coating that favors restoration of normal function and healing. By *helping the ulcer help itself,* Robalate provides a smooth therapeutic course for the ulcer patient.

A. H. ROBINS COMPANY, INC.
Richmond 20, Virginia

TABLETS **Robalate**®

(Dihydroxy aluminum aminoacetate, N.N.R., 0.5 Gm. per tablet)

CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION



a 30 second experiment

Drop a Syntrogel tablet in water. In less than 30 seconds you will note that it "fluffs up" to many times its size. This speedy disintegration increases the adsorptive surface approximately 10,000 times. Syntrogel goes to work in the stomach with equal speed. It adsorbs and neutralizes stomach acid, alleviates heartburn and provides prompt, yet long-lasting relief in most cases. Syntrogel gives symptomatic relief in peptic ulcer, dietary indiscretions and other conditions of gastric hyperacidity.

HOFFMANN-LA ROCHE INC • NUTLEY 10 • N. J.

Syntrogel®

Each Syntrogel tablet contains aluminum hydroxide, calcium carbonate, magnesium peroxide and Syntropan®.

'Roche'

Lubricoid action

WITHOUT OIL IN CONSTIPATION

Turicum combines methylcellulose in hydrated form with magnesium hydroxide in less-than-laxative dosage to maintain hydration throughout the bowel.

The methylcellulose passes through the stomach and small intestine without digestive breakdown; mixes with the fecal residue in the colon, incorporating dry particles in its mass.

The osmotic effect of magnesium hydroxide assures the presence of adequate water as the dry fecal material is brought into the gel. Thus easy passage is accomplished without stimulant cathartics.

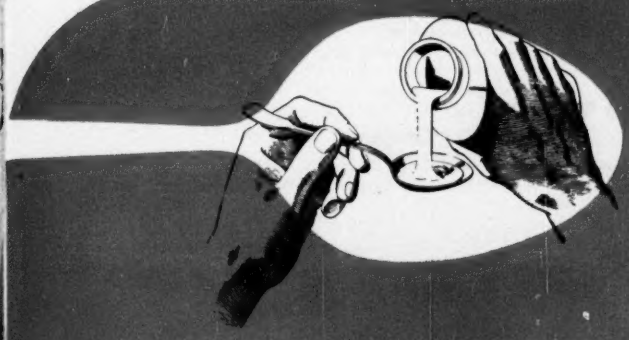
Turicum is unique as a non-oily lubricoid, fecal-softening agent, acting in a rational manner to restore the normal pattern of bowel function. With Turicum there is no bloating—no danger of impaction, lipid pneumonia or leakage, and no interference with utilization of oil-soluble vitamins.

***Average dose:** one to two tablespoonfuls.*

Available in pint bottles.

TURICUM®

HYDROPHILIC LUBRICOID



Whittier

LABORATORIES

DIVISION NUTRITION RESEARCH LABORATORIES, INC.

CHICAGO 11, ILLINOIS

The problem of

Intestinal Stasis

The physician finds in treating intestinal stasis that the patient has usually "doctored" himself for years with cathartics or enemas; his bowel habits may be bad; he is often convinced that not constipation but "something else" is wrong.

Despite these handicaps to therapy, the patient can be convinced that his condition is correctible, even where it has existed for years. But first he must accept the idea that he is being offered neither a "quick cure" nor mere temporary relief; that the goal of therapy is *correction.*

As corrective therapy, Cellothyl affords special advantage for it acts to rectify several common, often co-existing factors:

1. **bulk deficiency** ... *by providing adequate bulk of proper consistency*
2. **hypomotility** ... *by encouraging peristalsis through gentle mechanical stimulation*
3. **inspissation** ... *by retaining water*
4. **dyschezia** ... *by assuring soft, moist, easily passed stools.*

Normal, well-formed stools usually begin to appear in 3 to 4 days. However, bowel function improves markedly only when therapy is continued until Cellothyl's peristalsis-stimulating bulk achieves intestinal regularity.

Where an anticonstipation regimen is required, a simplified program is available in a small leaflet entitled "7 Rules for 7 Days". After outlining the faulty habits which cause intestinal dysfunction—poor diet, delayed defecation, etc.—it presents 7 simple rules to be followed for at least 7 days. To obtain copies: write "7 Rules" on a prescription blank and forward to Chilcott Laboratories, Morris Plains, New Jersey.

Cellothyl® BRAND OF METHYLCELLULOSE ESPECIALLY PREPARED BY THE CHILCOTT PROCESS

Available: Cellothyl Tablets *(0.5 Gram) in bottles of 100, 500 and 5000.*
Cellothyl Granules, *for pediatric use, in bottles of 25 and 100 Grams.*

CHILCOTT *Laboratories* DIVISION OF The Maltine Company
MORRIS PLAINS, NEW JERSEY

THE INTER-RELATIONSHIP BETWEEN CARDIOVASCULAR FUNCTION AND GASTRO-INTESTINAL DISEASE

EDWARD SUCKLE, M.D. and GEORGE K. WHARTON, M.D., Los Angeles, Calif.

THE SIMULATION OF cardiovascular disease by gastro-intestinal disease and vice versa presents problems in correct diagnosis and adequate treatment. At times pains of cardiac origin may be referred to the abdomen while those of abdominal origin may make their initial appearance in the thoracic region. The common innervation of both the thoracic and the abdominal organs by the autonomic nervous system accounts for these similarities of pain-reference. To clarify this problem the anatomy and physiology of the various organs will be reviewed as well as experimental work which has been done showing the effect of dysfunction of the gastro-intestinal tract and derangements of the autonomic nervous system on the heart. The various clinical conditions responsible for unusual pain-reference will be reviewed and illustrative cases presented.

A study of the inter-relationship between the heart and gastro-intestinal systems is best approached through an understanding of their nervous innervations. Both systems derive their nerve supply from the sympathetic and parasympathetic autonomic nervous system. The sympathetic innervation of the heart includes the cardiac plexus, the superior, middle, and inferior cardiac nerves, which arise from the superior, middle, and inferior sympathetic ganglia and also rami arising from the second, third, and fourth thoracic sympathetic ganglia. In addition, Kuntz (1) found in most of the bodies he dissected that the fifth and sixth thoracic sympathetic ganglia on both sides sent filaments to the cardiac plexus. The vagus supply to the heart consists of three rami on either side. The superior cervical ramus arises from the vagus trunk just distal to the origin of the superior laryngeal nerve. The inferior cervical ramus, the largest cardiac branch of the vagus, usually arises from the recurrent laryngeal nerve. The third or thoracic cardiac ramus arises from the vagus trunk within the thorax. The coronary arteries in their larger branches are supplied by both sympathetic and parasympathetic nerves, but Woolard's investigations led to the conclusion that the smaller branches and arterioles are innervated mainly by parasympathetic fibres, (the vagus). The gastro-intestinal tract is similarly innervated by the vagus and sympathetics. The pharynx in its upper portion is supplied by the glosso-pharyngeal, the ninth cranial nerve, and the remainder as stated before. It is only in the descending colon and rectum that the vagus supply is replaced by parasympathetic supply directly from the sacral spinal cord in its second, third, and fourth segments.

Afferent impulses arising from the heart and proximal aorta are conducted to the central nervous system via the sympathetics and the vagus. The experiments of White, Garrey and Atkins (2) indicated that cardiac impulses which eventuate in pain are conducted by sympathetic afferent fibres whereas impulses of cardiac origin conducted by the vagi do not give rise to pain. Sensory axones from the abdominal viscera run with the sympathetic nerves, primarily in the splanchnics. In the case of the esophagus the vagus is a sensory pathway, together with trigeminal and glossopharyngeal nerves. It is also believed that the sensation of nausea is in part carried by the vagus. The proof that pain sensations are carried mainly by the splanchnics is evidenced by the dramatic relief of abdominal pain afforded by sympathectomy.

The role of the vagus in vasoconstriction of the coronary artery was experimentally demonstrated by Anrep (3). Faradic stimulation of the peripheral end of one vagus resulted in marked diminution of the coronary flow, but on the other hand when both vagi were sectioned, coronary flow more than doubled. Wiggers (4) had previously made similar observations clinically. The effect of vagal stimulation was noted by Morrison and Swalm (5) in patients with angina pectoris. Balloon distention of the esophagus resulted in appearance of typical anginal pain and a depression of the ST segment in the electrocardiogram. Gilbert, Fenn and LeRoy (6) showed that moderate distention of the stomach in dogs caused a decrease in coronary flow. The decrease was greater when the distention affected primarily the cardiac end of the stomach. Section of the vagus or the administration of atropine abolished this reflex. Distention of the free abdominal cavity with air also resulted in a decreased coronary flow, which again did not appear after vagus section or atropine. Clinically, the same authors showed that patients with angina pectoris had a decreased Levy anoxemia tolerance after eating, but this was prevented by the prior administration of atropine. Morrison and Swalm (5) noted that distention of the stomach in one patient with angina resulted in cardiac standstill with immediate return to normal rhythm following relief of distention.

The reflex effect from the gall bladder on cardiac function in patients with angina pectoris was studied by Ravdin and his co-workers (7). The distention of the common duct by fluid forced through a T-tube reproduced the preoperative anginal pain whereas reduction of this intraductal pressure by amyl nitrite or cessation of flow relieved this pain. They concluded that reflexes arising in the extrahepatic bile passages may at times bring about a restriction in coronary flow resulting in the symptoms of angina pectoris. Bellet and Meade (8) attempted to produce significant changes in the electrocardiogram of the dog by distention of the gall bladder or the common duct. No change was obtained unless a small coronary vessel had previously been ligated in which case abnormalities in rhythm and conduction were obtained. Smith and Miller (9) have demonstrated in dogs that vagal reflexes may originate in the gall bladder, colon and appendix.

Prolonged vagal stimulation has been shown experimentally to cause myocardial damage. Hall, Ettinger

From the Department of Medicine of the University of Southern California School of Medicine, and the Los Angeles County Hospital.

Submitted March 23, 1951.

and Banting (10) gave 50 milligrams of the parasympathetic stimulant, acetylcholine, daily for one month to dogs. Systolic murmurs, electrocardiographic changes, and myocardial damage in the form of infarcts, and hyaline degeneration of the medium and smaller arteries resulted. Manning and his co-workers (11) did similar experiments by faradic stimulation of the vagus and their animals showed like changes in the heart. The animal which received atropine in addition to vagal stimulation showed no changes in the heart.

Disturbances of cardiac rhythm has long been noted with disease of the gall bladder. As early as 1908 Babcock (12) recorded several cases of cholecystitis with arrhythmias which disappeared after surgery. Strauss and Hamburger (13) also observed two cases with extrasystoles which disappeared after removal of an infected gall bladder. The experimental production of changes in cardiac rhythm was undertaken by Ivy (14), who found that administration of bile or bile salts in moderate dosage resulted in bradycardia, whereas atropine or vagal section abolished the heart slowing. He explained the increase in vagal tone in obstructive jaundice either by reflexes arising from distention of the biliary passages or by an increase in the bile salts. Crittenden and Ivy (15) later tested the vagotonic effect of apomorphine on dogs. During the retching phase, transient auriculo-ventricular block was noted in some animals, whereas in others there was a decrease in heart rate and in a few animals cardiac arrest up to 2.9 seconds occurred. The vomiting phase induced by this drug was accompanied by ectopic ventricular beats. The prior administration of atropine eliminated the cardiac inhibition and heart block. When jaundice was induced by ligation and section of the common bile duct, extrasystoles occurred during nausea, retching, or vomiting. The effect of apomorphine became more marked in these jaundiced animals with an increase in the number of electrocardiographic irregularities. Owens (16) distended the biliary passages of dogs by ligating the common duct and noted marked arrhythmias in three of the five unanaesthetized animals. These changes included sino-auricular block, bradycardia progressing to heart block, and auricular or ventricular ectopic beats. He was able to abolish the extrasystoles induced by belching by section of the vagi. Wakefield (17) demonstrated a viscerocardiac reflex in man by rapidly injecting 30 to 50 cubic centimeters of normal saline into the gall bladder with an impacted stone at the outlet. The resulting electrocardiographic effects in twenty-five patients were: extrasystoles (ventricular), increase in heart rate, prolongation of the PR interval and depression of T_2 in most cases. Complete heart block was noted in one case and another patient exhibited ventricular tachycardia of short duration.

CLINICAL

Pharynx

The act of swallowing my initiate such strong vagal impulses that cardiac function is seriously interfered with. In the case reported by Ray and Stewart (18) the subject suffered with typical glossopharyngeal neuralgia induced by swallowing and talking. Severe attacks were characterized by faintness and sometimes loss of consciousness. It was observed that during these severe attacks the patient developed asystole for several seconds followed by a bradycardia and a fall in systolic blood pressure of 25 to 30 millimeters of mercury for the duration of the pain. Section of the ninth cranial nerve within the skull abolished these attacks. The explanation for these attacks is not hard to find when it is realized that the vagus has numerous connections with the glossopharyngeal nerve, just as the tenth cranial nerve leaves the skull.

Esophageal Diverticulum

Irritation from an esophageal diverticulum may initiate a vago-vagal reflex resulting in heart block with ventricular standstill. Weiss and Ferris (19) reported a case of sudden dizziness or fainting lasting a minute or so precipitated by swallowing food. The electrocardiogram during these attacks showed complete auriculoventricular dissociation and ventricular standstill. A roentgenogram of the esophagus revealed a diverticulum in the lower third with dilatation of the esophagus in its lower portion. Distention of a balloon at the level of the diverticulum reproduced the symptoms of the attack and the change in the electrocardiogram already referred to. The administration of 1.0 milligram of atropine subcutaneously prevented the effect of balloon distention and the regular administration of atropine sulfate in doses of grains 1/120 three times a day prevented recurrent attacks. Ephedrine sulfate given every three hours was able to prevent syncope but balloon distention caused the electrocardiogram to change to auriculoventricular dissociation with the ventricles beating regularly. Thus, while the sympathomimetic stimulant insured the sensitivity of the ventricles to its own rhythmicity, the vagal stimulation caused by esophageal irritation was sufficient to make the auriculoventricular node refractory to impulses from the auricles.

Esophageal Spasm

Pain of esophageal origin is characteristically substernal in location with a burning, pressing or squeezing quality. Thus the distribution of the pain is so like that of angina pectoris that confusion of the two conditions is likely. In fact, Wolferth and Edeiken (20) are of the opinion that differentiation of anginal and esophageal spasm pain may be impossible on clinical grounds alone. They observed that the electrocardiogram was unaltered during the period of esophageal spasm whereas characteristic ST segment changes appeared during the attack of angina pectoris. Fluoroscopically the esophagus was found to be contracted in the former condition but no variation from normal was seen when the patient was suffering from a true anginal attack. Careful history, however, did reveal that the esophageal spasm was precipitated by smoking, eating, and nervous tension, whereas the anginal attack was characteristically provoked by physical effort and nervous tension. While amyl nitrite relieved both conditions, the relief was prompt in the coronary artery disorder and slow and somewhat uncertain in the spastic esophagus.

Diaphragmatic Hernia

Esophageal hiatal hernia is productive of symptoms in both chest and abdomen. Jones (21) studied 128 cases and found that while over half had epigastric pain and vomiting, substernal pain was a prominent symptom in over a third of his patients with small hernias. Interestingly enough, Olsen and Harrington (22)

found that a like percentage (32%) of their 220 patients also complained of substernal distress or burning. Jones (21) further noted that shoulder pain was present in 25% of all his patients and smaller numbers complained also of axillary, subscapular, back, and arm and hand pain. A few included dyspnea and palpitation with their symptoms. One-third of his patients with substernal pain stated that exertion frequently initiated the symptoms. Gilbert (23) also pointed out that the pain of recurrent esophageal hiatal hernia may be precipitated by carrying heavy articles. If the hernia becomes incarcerated and prolonged bleeding occurs from ulceration of the esophageal or stomach mucosa resulting in marked anemia, dyspnea, weakness and fainting may occur. Cough may appear when the patient assumes a recumbent position. Paroxysmal auricular fibrillation appearing with stooping down and lifting heavy weight or with lying in bed has been seen by Gilbert in several cases of hiatal hernia. It can be easily seen from the foregoing how an esophageal hiatal hernia may masquerade as a cardiac disorder.

The coexistence of angina pectoris and nocturnal anginoid pain from a small hiatal hernia is illustrated in the following case. Marked improvement of the cardiac condition resulted from measures directed to the hiatal hernia.

CASE NO. 1

This 58-year-old man reported to the Clinic with a history of chest pain on exertion for the past five years, dyspnoea on climbing one flight of stairs for two years. During the past year the patient suffered nocturnal angina characterized by substernal pain radiating to both shoulders, down both arms and to the interscapular region. These latter attacks invariably appeared after retiring and would last 30 to 40 minutes and were accompanied occasionally by dyspnoea.

Physical examination revealed an initial blood pressure of 170/95 but on subsequent occasions was 130/80. There was a systolic murmur in the mitral area in the left lateral position. Fluoroscopy showed the heart to be of normal size with an elongated aorta. The electrocardiogram showed a flat T_1, inverted T waves in V_1-V_3 and diphasic in V_4 to V_6. AV_1 showed a deep QS complex with T inverted. The interpretation was postero-lateral myocardial infarction—old, healed. The cardiac diagnosis was: Hypertensive arteriosclerotic cardiovascular disease. Fibrosis of myocardium with healed myocardial infarct. Angina pectoris, sinus rhythm, functional Class 3 and therapeutic Class D.

Within two weeks after being on aminophyllin, the patient reported improvement. However, because of symptoms of vomiting after breakfast, patient was referred to the gastro-intestinal clinic where a hiatus hernia was suspected. The first x-ray and fluoroscopy did not reveal a hiatal hernia. However, when the patient reported that relief of nocturnal angina came from sitting up, a second gastro-intestinal x-ray was requested three hours after recumbency. It was then that a small paraesophageal hiatal hernia was found. Corrective measures consisting of diet, antispasmodics and sedation were instituted. Occasionally nitroglycerin was employed at night. Patient subsequently reported over a six-month period that he could walk without angina of effort.

However, differentiation of esophageal hiatal hernia from true angina pectoris is made if careful attention is paid to the following points. The substernal distress of angina is most often brought on by effort, whereas this symptom in hiatal hernia is characteristically related to food ingestion, nervous tension, and appears often with recumbency after meals or after retiring for the night, and the patient finds relief when he arises and walks about. Arm radiation of the pain, of esophageal origin, is in the distribution of C_3, C_4, C_5, and when it extends to the hand is on the radial side rather than the characteristic ulnar distribution of anginal pain. Dysphagia is often a prominent symptom in hiatal hernia but is usually absent in angina. Epigastric pain may be the initial sign of coronary thrombosis but the accompanying shock, leucocytosis and EKG changes are absent in hiatal hernia. While nitroglycerin gives prompt relief to anginal pain, esophageal pain subsides slowly or not at all after taking this drug. The marked relief by atropine of both the substernal and epigastric distress is not seen in uncomplicated angina. Finally, the demonstration of the hiatal hernia by X-ray establishes the diagnosis. Unless the Trendelenberg position is employed and a careful and repeated search is made for the hernia, it may be missed. This is mentioned by Jones (21) who found it necessary to do three X-ray examinations on each of nine of his patients with esophageal hiatal hernia, before the lesion could be demonstrated.

Diaphragmatic hernia may be productive of anginal pain and electrocardiographic changes which appear with distention of the stomach and disappear with the stomach empty. The following case was observed by T. R. Van Dellen (24) and is illustrative.

CASE NO. 2

H. W., a 60-year-old white female, entered the hospital complaining of a small mass on the left breast of three months' duration. She also complained of occasional attacks of cardiac irregularity, with slight evening ankle oedema and slight dyspnoea on exertion.

Physical examination revealed a small mass on the left breast with dimpling of the areola. The heart did not seem enlarged nor were there any abnormalities except an accentuation of the aortic second sound and a blood pressure of 170/94.

Routine laboratory procedures including the serology were normal.

The patient was operated upon and when frozen-section diagnosis of carcinoma was established, the left breast was removed by radical mastectomy. The post-operative course was uneventful until the 13th post-operative day when the patient developed left scapular pain with questionable reference down the left arm. The blood pressure at that time was 136/80. Three days later the patient had a recurrence of the pain on arising and subsequently found that any exertion increased the pain. An electrocardiogram taken at that time showed a diphasic T_1 and a flattened T_2 and T_3. Two days later another electrocardiogram showed an inversion of T_2 and T_3 with a depression of the ST_2 as well as a deepened S_4. At this time the diagnosis of a coronary occlusion was considered. The next day on physical examination, dullness was elicited at the base of the left chest on percussion which two days previously, when the patient was distended, was quite tympanic. X-ray examination of the left chest revealed a large diaphragmatic hernia.

It was felt that electrocardiograms taken before and after eating might prove of interest. When the stomach was empty, the T waves and ST segments were normal; following breakfast there was a marked depression of T_1 and T_2 with a depression of ST_4.

Cardiospasm

The onset of cardiospasm may be initiated by a severe epigastric pain which radiates substernally to the neck, lower jaw and ears and sometimes to the arms. Pain may be associated with swallowing food but more often occurs independent of deglutition. It may be of such severity that hypodermic injections of morphine are required for relief. Little wonder that on clinical examination the early stages of the disease are confused with gall stone colic, angina pectoris or even coronary occlusion. When pain antedates the appearance

of other symptoms of cardiospasm, accurate diagnosis may be impossible (25). However, the electrocardiogram ordinarily does not reveal the characteristic changes associated with coronary artery insufficiency.

Instances of auricular fibrillation and heart block have been reported in these cases. In Iglauer and Schwartz's (26) patient cardiospasm was responsible for vago-vagal syncope. Swallowing in this subject resulted in momentary asystole followed temporarily by a slow heart rate found to be a 2:1 auriculoventricular block in the electrocardiogram. Ephedrine gave temporary relief and gradual bouginage relieved the attacks permanently.

In patients with coronary artery disease and angina pectoris, the pneumatic dilatation of the esophagus for cardiospasm is not without danger to the heart. This was observed by Morrison and Swalm (5) who noted ST segment depressions in the electrocardiogram, appearance of typical anginal attacks and cardiac standstill. These observations might explain the cause for sudden death in patients with cardiospasm. This would suggest the need for substantial doses of atropine or parasympathetic inhibitors to protect the heart.

STOMACH

Peptic Ulcer

The localization of pain in both gastric and duodenal ulcer usually follows a definite pattern. With the typical history the condition is readily diagnosed. Gastric ulcer usually manifests itself as a discomfort in the epigastrium somewhere between the xiphoid process and umbilicus, often to the left of the midline. When the gastric ulcer is of the perforating type, pain is present in the left upper quadrant, near the costal margin. Rivers (27) noted in 93% of his cases that when peptic ulcers invade the mesentery, mesocolon, or abdominal wall, there is a secondary shift of pain into the thorax or back.

The pain of duodenal ulcer is usually placed in the epigastric region, near the xiphoid process but may ordinarily be anywhere between the end of the sternum and the umbilicus. In the perforating type Rivers (27) noted a pain in the right upper quadrant in 90% of his cases.

The abdomen, however, is not the exclusive site for the pain of peptic ulcer. When radiation into the chest occurs, the resulting pattern is difficult to distinguish from a true angina pectoris. Levy and Boas (28) observed a number of patients with subsequently proven peptic ulcer who complained of epigastric burning with substernal radiation or radiation into the arms. The clue to the correct diagnosis was revealed in the history of periodicity after meals and relief by antispasmodics. On the other hand, true angina pectoris may be marked by epigastric localization with concomitant discomfort in chest or arms. Harrison (29) reported this in four of 77 cases of angina pectoris studied. Levy and Boas (28) noted that several patients who had suffered with peptic ulcer for many years with combined abdomino-thoracic distribution also showed the same pattern of pain when true angina made its appearance. In these cases the electrocardiograms revealed changes of myocardial infarction.

Sometimes the pain of peptic ulcer is exclusively thoracic and may be initiated by effort and relieved by rest. Clark (30) reported a case in a man, age 44, who suddenly developed severe substernal pain which was accentuated by exertion and relieved by rest. The appearance of shock and the lowered blood pressure (100/60) suggested a coronary accident. EKG showed a diphasic T_1 and a like change in the T waves of CR_4. No subsequent Q, R, or ST segment changes appeared, and the EKG became normal in several weeks. A gastro-intestinal X-ray revealed a duodenal ulcer and an ulcer regimen relieved the patient of his symptoms. Mixter's (31) case occurred in a physician, age 60. This patient suffered sharp stabbing pains starting in the back, encircling the chest around both sides to the sternum. All the attacks were related to exertion, excitement or fatigue. At times he complained of being unable to sleep on the left side. No gastro-intestinal symptoms were complained of and the electrocardiograms showed no significant changes. Even though the gastro-intestinal X-ray showed a duodenal ulcer and a small esophageal hiatal hernia, the physician-patient was adamant in his belief he had angina pectoris. Subsequently he developed a gastro-intestinal hemorrhage and with the institution of an ulcer regime, the anginoid symptoms disappeared.

Gastritis

A wide variety of symptoms has been ascribed to this clinical entity. For example: post prandial nausea sometimes with regurgitation and vomiting may suggest an obstructive lesion of neoplastic origin. Massive hematemesis may point to the possibility of a bleeding peptic ulcer. The early morning diarrhea which occurs in the atrophic variety makes the clinician suspicious of allergy or achlorhydria. But most of the chronic cases of gastritis are marked by a dull epigastric discomfort which does not radiate. However, Pardee (32) points out that the pain of gastritis may be situated high beneath the left pectoral area, may occasionally radiate to the lower retrosternal area or the episternal notch. Occasionally there may be radiation of pain and numbness into the left arm. This thoracic pain may be severe and griping and may "catch the breath." Pardee (32) points out that the pain often comes on spontaneously at night simulating nocturnal angina pectoris, or even, with severe pain, prostration, sweating and rapid pulse, suggesting coronary thrombosis. The relation of symptoms to physical effort, fullness or emptiness of the stomach serial electrocardiograms, gastroscopy and stomach X-ray will serve to differentiate the two conditions.

Miscellaneous Conditions of the Stomach

Chest pain arising from the stomach has been noted in a number of other conditions. Notable among these is a functional distention of the stomach arising from aerophagia, pylorospasm or ptosis of the stomach. Harrison (33) found thirteen patients with these disorders in whom pain was present at the lower end of the sternum, beneath the heart in the lower left chest, or in the precordium. The pain was ordinarily induced by eating or emotional disturbances and relieved by belching or expulsion of flatus, or by vomiting. Usually the act of belching or the administration of atropine produced the most striking relief. Sometimes the pain was stabbing in character and aggravated by breathing. In one patient the pain was aggravated by lying on the left

side. Although several patients gave a history of aggravation of pain on effort, severe effort under observation failed to reproduce the pain.

Cascade deformity of the stomach has been noted by several observers to cause chest pain in the form of oppression or pain in the lower left anterior chest coming on after eating or after exertion (34). Ordinarily the symptoms are those of epigastric fullness or of subxiphoid pressure. Harrison (33) pointed out that pain of cascade deformity may be precipitated by certain positions, especially the standing or sitting postures. The pain has a tendency to come on after small amounts of food are eaten and may disappear when additional food is swallowed. Similarly the deformity may be noted when only a small amount of barium is swallowed and disappear when the stomach is filled. Relief is usually obtained by lying on the left side but in some patients comfort is best achieved in the right lateral or prone positions. Other alleviating factors are belching, expulsion of flatus, and bowel movements. It is well to remember that many patients in whom the cascade deformity is discovered have no symptoms. In those patients with symptoms it is probably the aerophagic distention of the upper loculus (of the cascade deformity) that is responsible for the abdominal or thoracic discomfort.

In concluding the section on stomach conditions it might be worth mentioning that diverticulum of the stomach was indicated by Harrison (33) as the cause of pain with chest distribution in one case. All of Walters' (35) patients with gastric diverticula had their symptoms below the diaphragm.

Gall Bladder

It was the appearance of cardiac symptoms and signs during an attack of biliary colic that historically first marked the development of an interest in the possible relationship between the gastro-intestinal tract and the heart. In 1904 Osler (36) wrote in his *Practice of Medicine* that during an attack of biliary colic: "palpitation and distress about the heart may be present and occasionally a mitral murmur develops during the paroxysm." Riesman (37) in 1907 confirmed Osler's observations as to the presence of an apical systolic murmur and also noted increased cardiac dullness during or directly following an attack of gall stone colic in certain cases. Two years later Babcock (12) cited cases of chronic cholecystitis with pulse irregularities which were permanently relieved of the cardiac irregularities by removal of the inflamed gall bladder. Similarly systolic murmurs especially at the apex and "dilatation of the heart" were noted to subside with surgical treatment of the infected gall bladder.

That the course of cardiac disease might be favorably influenced by removal of an infected gall bladder was first pointed out by William Mayo (38). He described the case of a woman with "marked cardiac incompetency of the mitral type" confined to bed with dyspnoea and edema. She improved under a cardiac regime but later developed gall stone colic. Following removal of the gall bladder, there was no recurrence of cardiac decompensation. Willius and Fitzpatrick (39) analyzed the results of gall bladder surgery in 61 patients with both cholecystic and cardiovascular disease. There was an improvement in the cardiovascular condition in 54%. In only 7% did the cardiac condition appear to be adversely affected.

The simulation of angina pectoris by gall stones and biliary tract disease has been noted by a number of observers. Fitzhugh and Wolferth's (40) cases were marked by precordial pain, often severe, which sometimes radiated to the left shoulder and on occasions down the left arm. Most of their patients suffered attacks at night and only one had attacks induced by exercise. But all their cases had electrocardiographic changes characterized by inversion of T_2, inversion or lowering of T_1 and sometimes inversion of T_3. Tenderness over the gall bladder area or X-ray changes or development of a typical attack implicated the offending viscus. Removal of the gall bladder was followed by the return of the electrocardiogram to normal. Weiss and Hamilton (41) found four cases of cholecystitis and cholelithiasis with abnormal electrocardiograms consisting of convex ST_2 with T_2 inverted. Three of their four cases showed return of the electrocardiogram to normal after surgery—the fouth case having hypertensive cardiovascular disease. Breitweiser (42) also found T wave changes in 18 of his cases of cholecystitis (17 with cholelithiasis). Of the 50% who showed post-operative improvement of the electrocardiogram, the following were the pre-operative T wave changes: (1) low T_2; (2) low T in leads I, II and CR_5 and CR_6; (3) small and slightly inverted T waves in leads I and CR_5, together with a flat T_2. A prolongation of the PR interval to 0.30 second was observed in Moschowitz's case of gall stones. Cholecystectomy resulted in a return of the PR interval to within normal limits.

The mechanism of the production of precordial pain in biliary tract disease was demonstrated by Ravdin, Royster and Sanders (7), and has been previously referred to. It is interesting to note that the radiation of the precordial pain in one of their cases was down the ulnar aspect of the left arm. In another case the left chest pain with radiation to the left shoulder was produced by physical exertion or mental strain. Undoubtedly, as Ravdin has pointed out, some of these cases of gall bladder disease are associated with intrinsic disease of the coronary arteries and only with the reflex hyperactivity induced by the gall bladder is the cardiac disease made manifest.

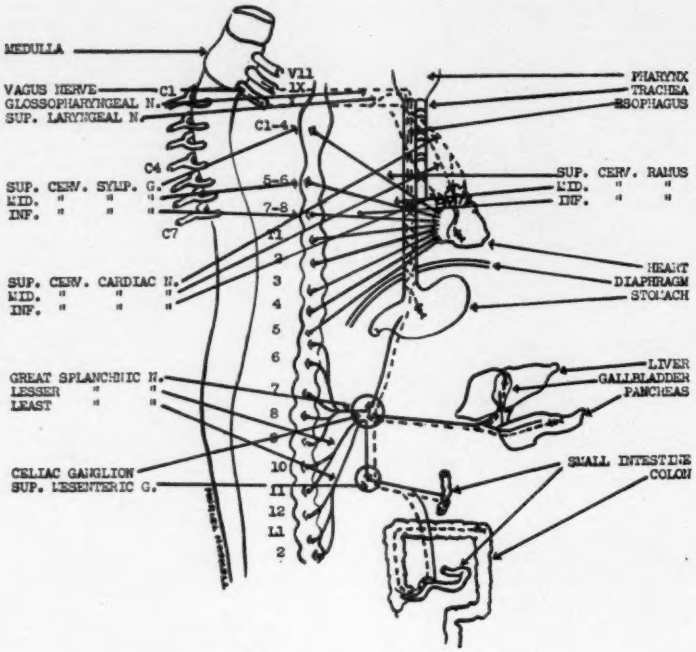
The following case is illustrative of the interaction of the cardiovascular and gall bladder systems:

CASE NO. 3

This 74-year-old man reported to the hospital with the complaint of pain in the right chest starting in October 1944. Pains became severe and vise-like with radiation to the throat, lasting ten minutes. Recently, the patient stated, these pains were brought on by exertion. However, since 1945 slight exertion evoked dyspnoea. There was also a history of epigastric distress one hour after meals containing such foods as sugars, fats, beans, cabbage and cream. Past medical history contained references to "heart attacks" five years ago and one year ago, but definitive information was not available.

Physical examination disclosed a blood pressure of 158/84 with systolic murmur at the aortic and pulmonic areas. Heart was normal in size. Rhythm regular and electrocardiogram revealed a right bundle branch block. In the abdomen the liver edge was palpable two finger breadths below the costal margin and over the right kidney region there was tenderness. An X-ray of the gall bladder showed a stone 1.5 centimeters in diameter and a subnormal concentrating power of the viscus.

A diagnosis was made of arteriosclerotic cardiovascular disease with coronary insufficiency, and angina pectoris with chronic cholecystitis and cholelithiasis. The patient was placed



INTER-RELATIONSHIP OF AUTONOMIC NERVE SYSTEM

on aminophyllin and nitroglycerin and within three weeks he reported the substernal pain had disappeared.

Since 1939 various abdominal complaints had been present. In 1944 food intolerance to gas forming foods was noted. In 1946 there was an attack of nausea and soreness in the epigastrium and right upper abdominal quadrant. Studies of blood amylase and urinary diastase were normal and after gastro-duodenal suction, condition subsided. Clinical impression at that time was an exacerbation of cholecystitis. During 1948 and 1949 the right subscapular pain assumed prominence. At times it was present on exercise. On other occasions the pain was described as a recurrent vise-like distress starting in the right subscapular region radiating around the body into the right upper quadrant and then upward in the substernal region. The patient then correlated the appearance of the pain in the upper right chest after eating mince pie and other foods to which he had become intolerant. On a gall bladder regimen he showed marked improvement and substernal pain was reported no longer present.

Another manifestation of reflex hyper-irritability in patients with biliary tract disease was demonstrated by Engel and Engel (43). They checked 23 patients with biliary tract disease for hyperactive carotid sinus reflex, characterized by asystole lasting a minimum of three seconds. A positive result was obtained in 78%. Post-operatively the hyperactive reflex disappeared in six of ten patients followed. Atropine sulfate 1.0 mgm. blocked the cardio-inhibitory reflex in all the cases treated. Thus the importance of the vagal component is involved. Their explanation for the hypersensitivity of the carotid sinus was based on the theory of summation of afferent impulses arising from afferent end-organs in the biliary tract, and not to the sensitization of the reflex itself. These observations would also afford a valid explanation for dizziness, syncope and even convulsions noted in attacks of biliary colic.

Pancreatitis

Acute pancreatitis is generally announced by pain in the upper abdomen, usually in the epigastrium or right upper quadrant. When the pain is in these sites, Paxton and Payne (44) found in their series of 307 cases that the necrotic process was found principally in the head of the pancreas. These observers noted that in several cases of acute pancreatic inflammation attacks were initiated by pain in the substernal region or in the precordium or in the left shoulder. In these instances of supra-diaphragmatic localization of pain pathologic studies revealed necrosis in the tail of the pancreas. One of the authors (GKW) has seen instances of diffuse pancreatitis with substernal pain radiation. Involvement of the left pleura and pericardium was noted by Paxton and Payne (44) in three of their cases. Similarly, Gottesman and Casten (45) observed a case of fat necrosis of the body of the pancreas with peritonitis and the presence within the precordial cavity of fifty cubic centimeters of brownish-red fluid. Such instances of direct precordial involvement are very uncommon. The reference of pain to the chest or shoulder obviously does not depend on direct extension of the inflammatory process beyond the abdominal region but is due to pain reference by reflex nerve pathways.

Electrocardiographic changes during acute pancreatitis were first reported by Gottesman, Casten and Bel-

ler (46) in 1942. Their cases revealed depression of the ST segments in limb leads 2 and 3, changes in the T waves of the limb and fourth lead varying from lowering to a diphasic contour or isoelectricity. T_1 often became inverted, and in some cases T_2 also showed the same change. It was the lowering of the ST segments and the decrease in amplitude of the T waves in several or all leads that occurred most frequently. Similar observations have been made by Bellet as reported by Bockhus (47). With the improvement in the clinical state, electrocardiogram reverted to normal.

Shock complicates about twenty percent of all cases of acute pancreatitis (44). The occurrence of upper abdominal pain with the manifestations of shock, low blood pressure, rapid thready pulse, acrocyanosis, gallop rhythm, muffled heart sounds coupled with electrocardiographic changes suggestive of beginning myocardial infarction and/or subendocardial ischemia could easily lead the clinician to a diagnosis of acute coronary thrombosis. However, the finding of an elevated blood amylase and corresponding increase in urinary diastase within the first 48 hours of the onset points to a diagnosis of acute pancreatitis. There are times when both acute pancreatitis and acute coronary thrombosis may coexist and only serial electrocardiographic studies and repeated serum enzymes (amylase at first, lipase after 48 hours) will reveal the true picture. Such a patient is unlikely to survive long enough for corroborative diagnostic measures. Fortunately, these instances are rare.

Peritonitis

When post-operative peritonitis is marked by the usual signs of generalized abdominal tenderness, distention, paralytic ileus, the onset of shock is not unexpected. But when anaerobic infection such as clostridium Welchii invades the peritoneum or extraperitoneal muscles after surgery, rupture of viscus or puncture wounds, the onset of shock may be fulminating and without sufficient local evidence of infection to suggest peritonitis (48). Little wonder that shock in this latter instance with all signs pointing to a rapid failure of the circulation should be attributed to a coronary insult of major proportions. A case of generalized post-operative peritonitis was reported by Averbruck (49) without physical signs of peritoneal infection or intra-abdominal hemorrhage. The shock picture and the electrocardiographic findings of low T_1 and low T_2 and tachycardia suggested acute coronary thrombosis. Necropsy, however, revealed patent coronary arteries and no evidence of myocardial infarction.

That electrocardiographic changes can be produced directly by peritonitis was demonstrated experimentally in dogs by Steinberg and his co-workers (50). They found depression of the ST interval and T-wave changes when the peritonitis was well-established.

Colon and Miscellaneous Conditions

The imprisonment of gas within a spastic colon in the splenic flexure may produce a most severe abdominal pain, radiating into the chest. The dyspnoea, tachycardia and pallor resulting from pressure on the diaphragm and consequent interference with unrestricted cardiac movement will suggest cardiac disease. Spasm of the colon may have its origin in diverticulitis or diverticulosis of the large bowel or in an autonomic imbalance without demonstrable alteration of bowel structure. To add to the difficulty of differentiation of pain arising from the colon accentuates the embarrassment to coronary circulation already impaired by the ravages of atherosclerotic disease (51). Actually the differentiation is not impossible if it is ascertained that the attack of abdominal pain from spastic colon is related to ingestion of food, nervous tension, constipation and relieved by expulsion of flatus, unloading of the bowel and release from nervous tension. The X-ray finding of spasm of the colon and/or changes indicative of diverticulosis or diverticulitis tends to be corroborative. The relief of pain by parasympathetic inhibitors such as atropine or atropine-like substances taken to the point of maximal tolerance points strongly in the direction of the large bowel being the provocative agent in the anginoid patient.

In conclusion the production of gastro-intestinal symptoms by cardiac disease should not be overlooked. Right upper quadrant pain from passive congestion of the liver, nausea and vomiting from engorgement of the stomach, ascites may be considered as due to intra-abdominal disease, whereas the real difficulty is right heart failure. The onset of myocardial infarction has been characterized in some instances by upper abdominal pain, usually epigastric, associated with localized tenderness (52). A study of 100 patients with myocardial infarct was recently made by Yeagley, Cayer and MacMillan (53). Forty had abdominal pain and disorders of digestion. Nearly all, or 35, localized their pain in the upper abdomen (the epigastrium being the principal site) with accompanying tenderness in most instances. While most of the patients had complaints directly referable to the cardiovascular system, seven per cent had only gastrointestinal complaints.

DISCUSSION

The displacement into the chest of symptoms originating in a diseased abdominal organ naturally focuses interest on the heart. This is particularly true when symptoms such as substernal distress, radiation of pain into the arms, and dyspnoea occur. Schrager and Ivy (54) quote Moynihan as having noted dyspnoea in 243 of 500 cases of gall stones, and experimentally, these investigators were able to produce inhibition of respiration by distention of the gall bladder or biliary ducts. T. R. Brown (55) describes such a case of progressive dyspnoea mistaken for cardiac disease until the true nature of the etiology became apparent with an attack of gall stone colic. It is the failure to recognize that the cardiovascular system may respond reflexly to extracardiac influences that the clinician is led into error. Another source of confusion is afforded by the history which is taken entirely along the line of gastrointestinal dysfunction, whereas the prominence of abdominal symptoms in sudden right heart failure might lead to an erroneous implication of the liver, or other organs, as the seat of disease in a true congestive failure.

The necessity for thorough investigation of both cardiovascular system and gastro-intestinal function is required when history is not typical and abdominal symptoms are present. Abnormal electrocardiograms alone or changes in the X-rays of the gastro-intestinal system do not suffice to implicate one system as totally responsible for the patient's symptoms. Unless a mul-

tilateral history is developed and then integrated with physical and laboratory findings, the result can be an erroneous emphasis on the organ acting reflexly.

Drugs which are commonly supposed to be specific in their effect on the cardiovascular system—such as amyl nitrite, aminophylline and papaverine—actually have a similar action on the smooth muscle of the gastrointestinal system. The initial therapeutic response is, therefore, misleading in some cases.

Proper therapeutic management of the diseased gall bladder, the colon made irritable by diverticulitis, or the stomach made hyperperistaltic by an active peptic ulcer serves to decrease the reflex vagotonia. Thus the cardiovascular system is spared a load which it can ill afford when it is already damaged.

There are four ways in which the abdominal organs may adversely influence the cardiovascular system. First, sudden increases in reflex vagotonia with consequent embarrassment of a cardiac coronary circulation not equal to sudden stresses. The occurrence of these instances in older patients is in keeping with the concept of vagotonia increasing with age. Secondly, abdominal distention if marked or acute dilation of the stomach or a large diaphragmatic hernia serve to diminish the vital capacity of the pulmonary system and may also interfere with the normally unrestricted motion of the heart. Third, the effect of electrolyte change such as occur in intestinal obstruction, removal of ascitic fluid, pancreatitis are reflected in alterations in the electrocardiogram. Finally, shock-producing states such as severe hemorrhage from a peptic ulcer or shock from a fulminating peritonitis can markedly depress cardiac function.

SUMMARY

1. The literature of cardiac and gastro-intestinal relationships is reviewed and illustrative cases presented.

2. The effect of reflex vagotonia on the coronary circulation is emphasized. Other methods of how the gastro-intestinal system may adversely affect the cardiovascular system are discussed.

3. Gastro-intestinal disease may mimic cardiac disease.

4. Correction of disease within the abdomen often serves to decrease cardiac load and improve circulatory function.

REFERENCES

1. Kuntz, Albert, *The Autonomic Nervous System*, 1934, Lea & Febiger.
2. White, J. C., Garrey, W. E., and Atkins, J. A., Cardiac Innervation: Experimental and Clinical Studies, Arch. Surg., *26*:765, 1933.
3. Anrep, G. V., The Regulation of the Coronary Circulation, Physiological Rev., *6*:596, 1926.
4. Wiggers, Am. J. Physiol. *24*:391, 1909.
5. Morrison, L. M. and Swaim, W.A., Role of the Gastro-Intestinal Tract in Production of Cardiac Symptoms, J.A.M. A. *114*:217, 1940.
6. Gilbert, N. C., Fenn, G. K., LeRoy, G. V., Effect of Distention of Abdominal Viscera on the Coronary Blood Flow and on Angina Pectoris, J. A. M. A. *115*:1962, 1940.
7. Ravdin, I. S., Royster, H. P., Sanders, G. B., Reflexes Originating in the Common Duct giving rise to Pain Simulating Angina Pectoris, Ann. Surg. *115*:1055, 1942.
8. Bellet, S., and Meade, R. H., Unpublished Observations.
9. Smith, F. M. and Miller, G. H., A Study of the Reflex Influence of the Colon, Appendix and Gall Bladder on the Stomach, Am. J. Physiol. *90*:518, 1929.
10. Hall, G. E., Ettinger, G. H., and Banting, F. G., An Experimental Production of Coronary Thrombosis and Myocardial Failure, Canad. M. A. J. *34*:9, 1936.
11. Manning, G. W., Hall, G. E., and Banting, F. G., Vagal Stimulation and the Production of Myocardial Damage, Canad. M. A. J. *37*:314, 1937.
12. Babcock, R. H., Chronic Cholecystitis as a Cause of Myocardial Incompetence, J. A. M. A. *52*:1904, 1909.
13. Straus, D. C. and Hamburger, W. W., The Significance of Cardiac Irregularities in Reference to the Operability of Cases of Cholelithiasis, Cholecystitis and Duodenal Ulcer, J. A. M. A. *82*:706, 1924.
14. Ivy, A. C., Physiologic Disturbances Incident to Obstructive Jaundice, J. A. M. A. *95*:1068, 1930.
15. Crittenden, P. J., and Ivy, A. C., A Study of Viscerocardiac Reflexes, Am. Heart J. *8*:507, 1933.
16. Owens, S. E., A Study of Viscerocardiac Reflexes, Am. Heart J. *8*:496, 1933.
17. Wakefield, H., The Association of Gall Bladder Disease with Heart Disease: Clinical and Experimental Observations, Med. Clin. N. A. *31*:161 (Jan.) 1947.
18. Ray, B. S., and Stewart, H. J., Glossopharyngeal Neuralgia: A Cause of Cardiac Arrest, Am. Heart J. *35*:458, 1948.
19. Weiss, S., and Ferris, E. B., Jr., Adams-Stokes Syndrome with Transient Complete Heart Block of Vago-vagal Reflex Origin, Arch. Int. Med. *54*:931, 1934.
20. Wolferth, C. C., and Edeiken, J.: Differential Diagnosis of Angina Pectoris, with Special Reference to Esophageal Spasm and Coronary Occlusion, Penn. M. J. *45*:579, 1942.
21. Jones, C. M., Hiatus Esophageal Hernia (Comparison of its Symptoms with those of Angina Pectoris), New Eng. J. Med. *225*:963, 1941.
22. Olsen A. M. and Harrington, S. W., Esophageal Hiatal Hernias of the Short Esophagus Type: Etiologic and Therapeutic Considerations, J. Thoracic Surg. *17*:189, 1948.
23. Gilbert, N. C., Recurrent Esophageal Hiatus Hernia, Med. Clin. N. A. *32*:213, (Jan.) 1948.
24. Van Dellen, T. R., Personal Communication, 1949.
25. Vinson, P. P., *Diseases of the Esophagus*, C. C. Thomas, 1940.
26. Iglauer, S. and Schwartz, B.A., Heart Block Periodically Induced by the Swallowing of Food in a Patient with Cardiospasm (Vago-vagal Syncope), Ann. Otol. Rhin. and Laryn. *45*:875, 1936.
27. Rivers, A. B., "Peptic Ulcer," *Cyclopedia of Medicine, Surgery and Specialties*, Vol. 14, p. 340, 1939, F. A. Davis Co., Philadelphia.
28. Levy, H., and Boas, E. P., Angina Pectoris and the Syndrome of Peptic Ulcer, Arch. Int. Med. *71*:301, 1943.
29. Harrison, T. R., Clinical Aspects of Pain in the Chest. I, Angina Pectoris, Am. J. Med. Sci. *207*:561, 1944.
30. Clark, N. E., Electrocardiographic Changes in Active Duodenal and Gall Bladder Disease, Am. Heart J. *29*:628, 1945.
31. Mixter, W. J., Back Pain in Lesions of the Gastro-Intestinal Tract, with Particular Reference to Duodenal Ulcer, Am. J. Digest, Dis. and Nutrition *4*:736, 1937.
32. Pardee, E. B., Cardiac Manifestations of Gastro-Intestinal Disease, Rev. Gastroenterology *16*:395, 1949.
33. Harrison, T. R., Clinical Aspects of Pain in the Chest. III, Pain arising from the Stomach, Am. J. Med. Sci. *209*:771, 1945.
34. Bockus, H. L., *Gastro-Enterology*, W. B. Saunders, Phila., 1943, Vol. 1, p. 781.
35. Walters, W., Diverticula of the Stomach, J. A. M. A. *131*: 954, 1946.
36. Osler, W., *Practice of Medicine*, Appleton-Century, 1901, p. 564.
37. Riesman, D., Development of Cardiac Murmurs during Attacks of Biliary Colic, J. A. M. A. *48*:1589, 1907.
38. Mayo, William J., Certain Medical and Surgical Aspects of Disease of the Biliary Apparatus, Illinois Med. J. *45*:33, 1924.
39. Willius, F. A. and Fitzpatrick, J. M., The Relationship of

Chronic Infection of the Gall Bladder to Disease of the Cardiovascular System, J. Iowa State Med. Soc. *15*:589, 1925.

40. Fitzhugh, T. Jr., and Wolferth, C. C., Cardiac Improvement following Gall Bladder Surgery, Ann. Surg. *10*:478, 1935.
41. Weiss, M. M. and Hamilton, J. E., The Effect of Gall Bladder Disease on the Electrocardiogram, Surgery *6*:893, 1939.
42. Breitweiser, E. R., Electrocardiographic Observations in Chronic Cholecystitis before and after Surgery, Am. J. Med. Sci. *213*:598, 1947.
43. Engel, G. L. and Engel, F. L., The Significance of the Carotid Sinus Reflex in Biliary Tract Disease, New Eng. J. Med. *227*:470, 1942.
44. Paxton, J. R. and Payne, J. H., Symptoms of Acute Pancreatitis, California Med. *67*:241, 1947.
45. Gottesman, J., and Casten, D., Changes in the Electrocardiogram induced by Acute Pancreatitis, J. A. M. A. *123*:892, 1943.
46. Gottesman, J., Casten, D., Beller, A. J., Electrocardiographic Changes Associated with Acute Pancreatitis, Proc. Soc. Exper. Biol. and Med. *49*:365, 1942.
47. Bellet, S., quoted by Bockus, H. L., *Postgraduate Gastroenterology*, W. B. Saunders, Phila., 1950, pp. 330-333.
48. Davis. H. A., Personal Communication, 1950.
49. Averbruck, S. H., Acute Generalized Peritonitis Simulating Coronary Artery Occlusion, J. Mt. Sinai Hosp., *8*:335, 1942.
50. Steinberg, B., et al., Proc. Soc. Exper. Biol. and Med. *30*: 1155, 1933.
51. Fenn, G. K., Pain Simulating that of Coronary Disease, Med. Clin. N. A. *19*:1077, 1936.
52. Levine, S. A. and Tranter, C., Infarction of the Heart Simulating Acute Surgical Abdominal Conditions, Am. J. Med. Sci. *155*:57, 1918.
53. Yeagley, J. D., Cayer, D. and MacMillan, R. L., Gastrointestinal Symptoms in Coronary Heart Disease, N. Carolina Med. J. *10*:22, 1949.
54. Schrager, V. L., and Ivy, A. C., Symptoms Produced by Distention of the Gall Bladder and Biliary Ducts, S. G. O. *47*:1, 1928.
55. Brown, T. R., Cardiac Symptoms in Unsuspected Gall Bladder Disease, *Libman Anniversary Volume I*, 1932, p. 265.

A CLINICAL STUDY OF THE PATHOGENESIS OF THE DIABETIC SYNDROME: USE OF A MODIFIED GLUCOSE INSULIN TOLERANCE TEST COMBINED WITH THE CHANGE OF SERUM INORGANIC PHOSPHORUS AFTER GLUCOSE ADMINISTRATION

BRUNO W. VOLK, M.D. and SYDNEY S. LAZARUS, M.D. Brooklyn, N. Y.

IN recent years it has been emphasized that the syndrome of diabetes mellitus may not be based solely on primary insulin deficiency, but also may be due to dysfunction of the anterior-pituitary (1), of the adrenal cortex (2), of the thyroid gland (3), or may be secondary to hepatic disorders (4, 5), or to certain other factors such as neurological disturbances (6, 7), to obesity (8), to infection (9), etc. The diagnosis of the diabetic syndrome is usually based on the glucose tolerance test (G.T.T.), which, although it does detect hyperglycemia unresponsiveness, throws no light on the pathogenesis of the impairment of carbohydrate tolerance.

In 1936 Himsworth (10) introduced the glucose insulin tolerance test (G.I.T.T.) which consists of the simultaneous administration of a standard glucose dose orally, and a standard insulin dose, intravenously. The response to this procedure is supposed to be a flat blood sugar curve in the normal individual and in some diabetics, and a curve similar to the G.T.T. in other diabetic individuals. On the basis of these different curves Himsworth divided the diabetic syndrome into an insulin sensitive type, which he attributed to insulin deficiency, and an insulin insensitive type, which he thought to be due to "lack of an unknown factor which sensitizes the organism to the action of insulin."

Fraser et al (11) in 1941 utilized the G.I.T.T. to differentiate whether the hyperglycemia unresponsiveness elicited by the G.T.T. in diabetic patients is due to insulin lack, or to insulin resistance, and concluded that in hypoinsulin diabetes the G.I.T.T. will be normal, whereas in diabetes due to hyperadrenocorticism and hyperpituitarism a curve similar to the G.T.T. will be found. However, these authors did not consider hepatic dysfunction as a pathogenetic factor in the production of insulin resistant diabetes, as has been suggested by other investigators (12). In reviewing our results obtained with the G.I.T.T., in a series of control cases, we observed that 6 out of 17 individuals showed a marked deviation from the normal pattern although no evidence of any endocrine abnormality or disturbance in carbohydrate metabolism was present. Moreover, it has been reported that in patients with acromegaly and diabetes (11) the G.I.T.T. may be either of the type of insulin sensitivity or insulin resistance, even though theoretically only the latter response should be obtained. In order to obviate these objections a modification of Himsworth's G.I.T.T. was substituted in which the standard dose of insulin was administered 30 minutes after the glucose, instead of simultaneously.

This procedure appeared more satisfactory since with it a uniform pattern of response was observed in 25 non-diabetic control persons, in contrast to the variable response obtained with the original G.I.T.T. It may be that the intravenous administration of both the glucose and insulin eliminates aberrations due to differing rates of intestinal absorption of glucose. Also, the body mechanisms for hyperglycemia responsiveness, which are stimulated by the administration of glucose, are set in motion before the insulin is in-

From the Division of Laboratories and the Department of Medicine, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, New York.

Submitted March 8, 1951.

jected, so that the added insulin acts in conjunction with these mechanisms rather than in opposition to them, as it does in Himsworth's G.I.T.T. We believe the modified G.I.T.T. to be therefore a sensitive indicator for the ability of the body to lower the blood sugar rapidly under the influence of a standard insulin dose.

In the normal individual a decline of the serum inorganic phosphorus after glucose administration is observed (13, 14). This phosphorus response occurs also in the hepatectomized but not in the visceral animal (15), and has been assumed, therefore, to be a significant indicator for peripheral glucose utilization. On this basis Forsham and Thorn (16) used it to differentiate a diabetes associated with normal peripheral glucose utilization, which was assumed to be due to hepatic dysfunction, from one associated with deficient peripheral glucose utilization, which was considered to be the result of either relative or absolute insulin deficiency. That such a differentiation may be made is supported by the fact that depancreatized humans (16) do not show a decline of serum inorganic phosphorus after glucose administration.

It was thought, therefore, that these two procedures might be used in combination for differentiating three pathogenetic factors of the diabetic syndrome, inasmuch as the change of the serum inorganic phosphorus would divide diabetes into one secondary to endocrine imbalance from one due to hepatic dysfunction, and the modified G.I.T.T. would indicate whether the endocrine imbalance was due to preponderance of insulin antagonists or to hypoinsulinism. The present report embodies such a study.

METHODS:

For the G.T.T. and the change in serum inorganic phosphorus level, fourteen fasting known diabetic patients received 25 gms of glucose as 50% solution intravenously. Immediately before and at intervals of 30, 60, 120, and 180 minutes after the administration of glucose capillary blood samples were collected for glucose and venous blood for serum inorganic phosphorus determinations. For the modified G.I.T.T., 25 gms of glucose in 50% solution was given intravenously followed by 0.1 unit of crystalline insulin per kilo body weight intravenously after 30 minutes. Capillary blood samples for glucose determination were withdrawn at fasting and at 30, 50, 60, 75, 90, 120, 150,

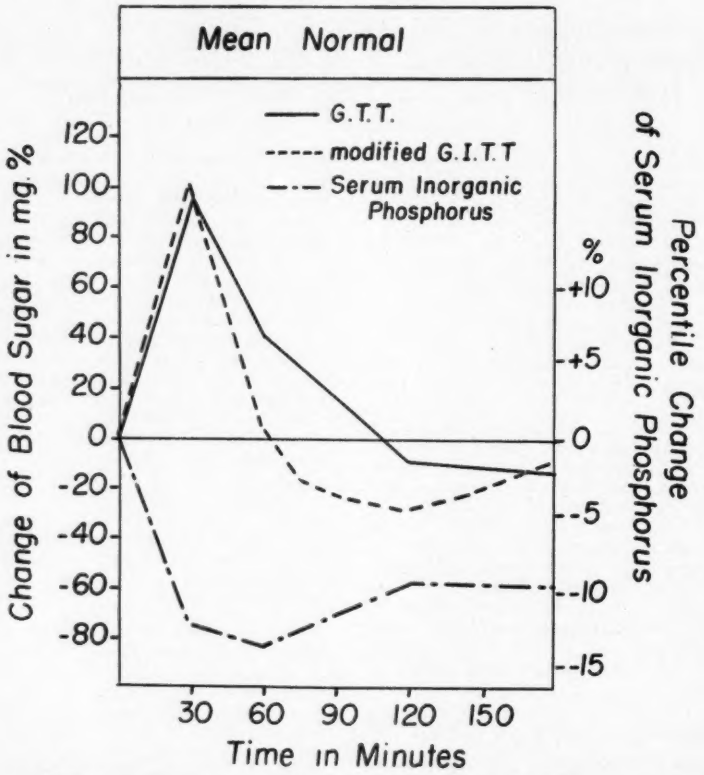


Figure 1. Mean curves for the G.T.T., the modified G.I.T.T. and the change in serum inorganic phosphorus observed in 25 normal individuals.

and 180 minutes after the administration of glucose. The blood sugar determinations were done by the Nelson modification of the Folin-Wu micro method (17). The serum inorganic phosphorus was performed by the method of Fiske and Subbarow (18). Similar procedures were carried out in 25 non-diabetic individuals who served as controls.

RESULTS:

G. T. T. The criteria for a normal G.T.T. were a fasting glucose level below 140 mg%, a rise to a maximum in 30 minutes with a return of the level to, or below, fasting value at, or before, 120 minutes after glucose administration (19). While all controls satisfied these criteria, none of the diabetic patients did.

Modified G.I.T.T. In the non-diabetic control persons the rise of the blood sugar level after intravenous glucose administration was similar to that seen in the ordinary G.T.T. In these cases the administration of insulin 30 minutes after the glucose, i.e., at the peak of the hyperglycemia, was followed by an immediate decline of the blood sugar value, with the fasting level reached within 30 minutes after the insulin was administered in all but two, in whom it was reached at 45 minutes. Therefore, our criterion for normalcy in the modified G.I.T.T. is a return of the blood sugar level to, or below, fasting level within 45 minutes after insulin (i.e., 75 minutes after glucose) administration (Fig. 1).

Of the fourteen diabetic patients, 4 showed a decline of the blood sugar to fasting values within 30-45 minutes after insulin administration. In the remaining 10 patients the blood sugar did not decline to the fasting level until 60 to 150 minutes after insulin. Neither the peak, nor the nadir, of the blood sugar seemed to be of significance for the evaluation of the curve.

Serum Inorganic Phosphorus. With the type of

TABLE I.

POSSIBLE PATHOGENETIC FACTORS OF THE DIABETIC SYNDROME IN 14 PATIENTS AS INFERRED FROM THE MODIFIED G.I.T.T. AND THE CHANGE OF SERUM INORGANIC PHOSPHORUS ("P") AFTER GLUCOSE ADMINISTRATION

Patient	Clinical Diagnosis	Modified G. I. T. T. Return of Blood Sugar to Fasting Level After Insulin (Time in Minutes)	Serum Inorganic "P." Maximum % Decline After Glucose	Interpretation	Possible Etiologic Factors
1. B.S.	Rheumatoid Arthritis with Hepatitis after Chrysotherapy	120	—12.4%	Insulin resistance with normal "P" decline	Liver dysfunction
2. E.R.	Diffuse Sclerosis of C. N. S.	60	—18.3%	Insulin resistance with normal "P" decline	Liver dysfunction
3. F.G.	Gen. Arteriosclerosis with Hypertensive C. V. Disease	60	—13.4%	Insulin resistance with normal "P" decline	Liver dysfunction
4. A.W.	Gen. Arteriosclerosis, Nephrosclerosis, Azotemia	60	—10 %	Insulin resistance with normal "P" decline	Liver dysfunction
5. J.B.	Adenocarcinoma of rectum with liver metastases	30	—10.7%	Normal insulin sensitivity with normal "P" decline	Probable liver dysfunction, but not conclusive
6. A.K.	Gen. Arteriosclerosis, Hypertensive C. V. Disease	150	—5.7%	Insulin resistance with abnormal "P" decline	Overactivity of insulin antagonists
7. F.E.	Gen. Arteriosclerosis with Wet Gangrene of Lower Extremity	90	—7.5%	Insulin resistance with abnormal "P" decline	Overactivity of insulin antagonists
8. K.S.	Gen. Arteriosclerosis, Hypertensive C. V. Disease	90	—0.1%	Insulin resistance with abnormal "P" decline	Overactivity of insulin antagonists
9. P.S.	Gen. Arteriosclerosis	60	0	Insulin resistance with abnormal "P" decline	Overactivity of insulin antagonists
10. L.G.	Paget's Disease of Bone	90	—6 %	Insulin resistance with abnormal "P" decline	Overactivity of insulin antagonists
11. I.M.	Congenital Hypothyroidism	60	—8.6%	Insulin resistance with abnormal "P" decline	Overactivity of insulin antagonists
12. L.S.	Gen. Arteriosclerosis, Hemiplegia	45	—3.7%	Normal insulin sensitivity with abnormal "P" decline	Probable hypoinsulinism, but not conclusive
13. C.B.	Gen. Arteriosclerosis, Hypertensive C. V. Disease	30	—3.7%	Normal insulin sensitivity with abnormal "P" decline	Probable hypoinsulinism, but not conclusive
14. M.C.	Gen. Arteriosclerosis, Hypertensive C. V. Disease	45	—5.4%	Normal insulin sensitivity with abnormal "P" decline	Probable hypoinsulinism, but not conclusive

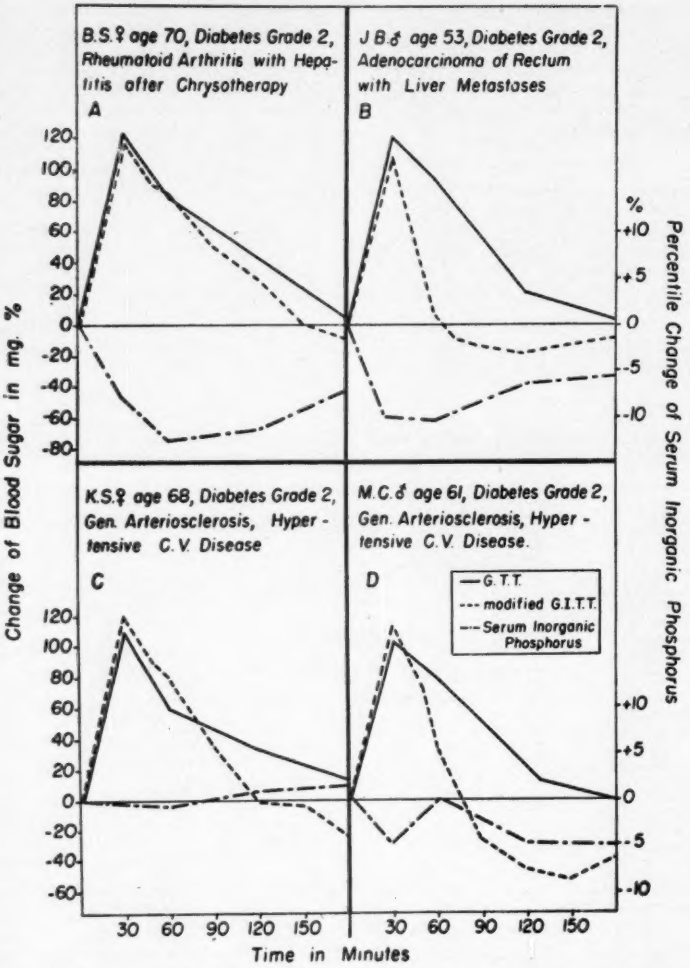

B.S.♀ age 70, Diabetes Grade 2, Rheumatoid Arthritis with Hepatitis after Chrysotherapy
A
J.B.♂ age 53, Diabetes Grade 2, Adenocarcinoma of Rectum with Liver Metastases
B
K.S.♀ age 68, Diabetes Grade 2, Gen. Arteriosclerosis, Hypertensive C.V. Disease
C
M.C.♂ age 61, Diabetes Grade 2, Gen. Arteriosclerosis, Hypertensive C.V. Disease.
D
G.T.T.
modified G.I.T.T.
Serum Inorganic Phosphorus
Change of Blood Sugar in mg. %
Percentile Change of Serum Inorganic Phosphorus
Time in Minutes

Figure 2. Patterns of the G.T.T., the modified G. I. T. T. and the change in serum inorganic phosphorus in 4 diabetic patients representing the 4 types of response obtained in a series of 14 diabetic patients.

G.T.T. used by us, all controls showed a maximum decline of serum inorganic phosphorus which varied from -10% to -22.5%. Of the diabetic patients, 5 showed a decline of serum inorganic phosphorus, similar to that observed in the normal, whereas the other 9 patients showed either no drop at all, or a drop which varied from -3.7% to -8.6%.

As seen from Table I, insulin resistance combined with a normal decline of the serum inorganic phosphorus was observed in 4 patients. Insulin resistance in the presence of a smaller than normal decline of the serum inorganic phosphorus was noted in 6 patients, a normal insulin sensitivity with a normal phosphorus decline was observed in one case, and a normal insulin sensitivity with an abnormal phosphorus decline was found in 3 patients.

DISCUSSION

As previously pointed out, the glucose tolerance test is a crude tool which reveals disturbances of normal blood sugar homeostasis without indicating the causative factors. However, we believe that the change in serum inorganic phosphorus level after glucose administration in combination with the modification of Himsworth's G.I.T.T. introduced by us can be used as a means to distinguish the pathogenetic factors un-

derlying the diabetic syndrome. Thus, insulin resistance combined with a normal decline of the serum inorganic phosphorus would indicate diabetes secondary to hepatic dysfunction, while in the presence of a smaller than normal inorganic phosphorus decline, it is indicative of a diabetes due to overactivity of insulin antagonists. On the other hand, a normal insulin sensitivity with an abnormal phosphorus decline is probably due to primary pancreatic insufficiency, but overactivity of insulin antagonists cannot definitely be ruled out. A normal phosphorus decline with a normal insulin sensitivity is suggestive of liver dysfunction diabetes. This combination, however, is not conclusive, since according to previous reports disturbance of liver function may be associated with insulin resistance (12).

A comparison of the clinical diagnosis with the experimental findings would in general support the inferences as to the pathogenesis in the individual patient. Of the 5 patients thought to have disturbance of carbohydrate metabolism due to liver dysfunction, 3 gave histories suggestive of hepatic disease prior to the onset of diabetes, one had had hepatitis after chrysotherapy, one had liver metastases secondary to an adenocarcinoma of the rectum, and one had azotemia due to nephrosclerosis, which is also associated with hepatic dysfunction (20, 21). In the other two patients there was no evidence suggestive of liver disease anteceding the onset of their diabetes. The remainder of the patients who were thought to have either relative or absolute insulin deficiency had clinical findings consistent with this hypothesis (Table I).

The four types of response elicited in this series by the combination of these two tests are illustrated graphically in Fig. 2, as compared to the mean normal curves shown in Fig. 1. Fig. 2A shows a modified G.I.T.T. in which the blood sugar did not decline to fasting within 90 minutes, and which is almost identical with the G.T.T. indicating insulin resistance. In this case the phosphorus decline is normal, showing that the insulin resistance is not endocrine in origin and therefore that the patients' diabetes is probably based on liver dysfunction. This is borne out by the clinical history, since the patient developed diabetes 6 months after a bout of hepatitis secondary to previous chrysotherapy for rheumatoid arthritis.

Fig. 2B illustrates a normal serum inorganic phosphorus decline in the presence of a diabetic G.T.T. but associated with a normal modified G.I.T.T. The normal phosphorus decline indicates normal peripheral glucose utilization, and therefore liver dysfunction diabetes. However, in view of the normal insulin sensitivity the results have to be considered as inconclusive. It is interesting to note, however, that this patient's diabetes was discovered 2 months after he was found to have adenocarcinoma of the rectum with liver metastasis.

Fig. 2C demonstrates a failure of decline of serum inorganic phosphorus after glucose administration which indicates decreased peripheral glucose utilization and therefore an endocrine diabetes. This is accompanied by an abnormal modified G.I.T.T. similar in shape to the G.T.T., indicating insulin resistance and suggesting that the diabetic syndrome in this patient is due to overactivity of insulin antagonists.

Fig. 2D demonstrates a normal insulin sensitivity in the presence of an abnormal serum inorganic phosphorus decline. The latter indicates an endocrine disturbance, while the normal insulin sensitivity suggests that this endocrine disturbance is pancreatic in origin. This inference is in accordance with the previously developed hypothesis of Himsworth (10) and Fraser et al. (11). It is believed, however, that a normal insulin sensitivity does not necessarily indicate hypoinsulin diabetes, since the standard dose of insulin used may be just sufficient to overcome the action of the insulin antagonists in some patients. It is of interest that even if these 3 cases were considered to be diabetic due to primary pancreatic insufficiency, they still constitute only about 25% of the patients studied. This would be in agreement with the reports of previous workers (22, 23, 24, 25) who believe that the human diabetic syndrome is in most cases not primarily an insulin-deficiency disease.

The information derived from these two tests may be of practical value in the treatment of the diabetic syndrome and clinical studies to this end are now in progress. For example, patients with liver dysfunction diabetes may benefit from therapy directed to the liver, and patients with diabetes secondary to overactivity of insulin antagonists may benefit from treatment which would tend to suppress anterior pituitary function. It should be remembered that in the past, attempts have been made to treat diabetics with regimens directed at compensating hepatic dysfunction by use of lipotropic substances, vitamin B complex, etc. (4, 26) or at suppression of pituitary activity by estrogens or androgens (27, 28, 29). In most of these studies a certain percentage of successes were reported; however, because of inability to differentiate the particular case in which treatment might be successful, these methods of therapy have more or less fallen into disrepute.

SUMMARY

A modification of Himsworth's G.I.T.T. is introduced which consists of the administration of 0.1 units of crystalline insulin intravenously 30 minutes after the intravenous injection of 25 Gms of glucose in 50 per cent solution. This procedure elicited a consistent pattern of response in the 25 normal individuals, the blood sugar falling to fasting level within 45 minutes after the insulin administration. This test in combination with the determination of the serum inorganic phosphorus decline after glucose administration promises to provide a clinical means of distinguishing three pathogenetic factors of the diabetic syndrome: hepatic dysfunction, overactivity of insulin antagonists and, by exclusion, primary insulin deficiency. It is suggested that this differentiation may be of practical value for the treatment of the diabetic syndrome.

REFERENCES

1. Coggeshall, C. and Root, H. F., Acromegaly and diabetes mellitus. Endocrinology, 26:1-25, 1940.
2. Russi, S., Blumenthal, H. T. and Gray, S. H., Small adenomas of the adrenal cortex in hypertension and diabetes. Arch. Int. Med., 76:284-291, 1945.
3. Foster, D. P. and Lowrie, W. L., Diabetes mellitus associated with hyperthyroidism. Endocrinology, 23:681-691, 1938.
4. Taub, S. J., Shlaes, W. H. and Rice, L., Liver dysfunction

hyperglycemia: Its etiology and relation to diabetes mellitus. Ann. Int. Med., 22:852-862, 1945.
5. Rabinowitch, I. M., The incidence of diabetes mellitus in diseases of the gallbladder and its passages. Canad. M. A. J., 14:296-297, 1924.
6. Best, C. H. and Taylor, N. B., Physiological basis of medical practice. Baltimore, Williams and Wilkins, p. 681, 1950.
7. Peter, J. P. and Van Slyke, D. D., Quantitative Clinical Chemistry, Vol. 1, Baltimore, Williams and Wilkins, p 252, 1946.
8. Rynearson, E. H. and Gastineau, C. F., Obesity, Springfield, C. C., Thomas, p. 19, 1949.
9. Williams, J. L. and Dick, G. F., Decreased dextrose tolerance in acute infectious diseases. Arch. Int. Med., 50:801-818, 1932.
10. Himsworth, H. P., Diabetes mellitus; its differentiation into insulin-sensitive and insulin-insensitive types. Lancet, 1: 127-130, 1936.
11. Fraser, R., Albright, F. and Smith, P. H., Carbohydrate metabolism: The value of the glucose tolerance test, the insulin tolerance test and the glucose insulin tolerance test in the diagnosis of endocrinologic disorders of glucose metabolism. J. Clin. Endocrin., 1:297-307, 1941.
12. Soskin, S. and Levine, R., Carbohydrate metabolism. Chicago, University of Chicago Press, p. 284, 1946.
13. Barrenscheen, H. K., Doleschall, F. and Popper, L., Beiträge zum Problem des Blutzuckers. VI. Mitteilung: Blutzucker-und Phosphorsäurekurve. 4. Diabetes., Biochem. Ztsch., 177:76-80, 1926.
14. Hartman, F. W. and Bolliger, A., Curve of inorganic blood phosphates during the sugar tolerance test. Significance in diagnosis and prognosis. J. A. M. A., 85:653-656, 1925.
15. Pollack, H., Millet, R. F., Essex, H. E., Mann, F. C. and Bollman, J. L., Serum phosphate changes induced by injection of glucose into dogs under various conditions. Am. J. Phys., 110:117-122, 1934.
16. Forsham, P. H. and Thorn, G. W., Changes of inorganic serum phosphorus during the intravenous glucose tolerance test as an adjunct to the diagnosis of early diabetes mellitus. Proc. Am. Diab. Assoc., 9:101-122, 1949.
17. Nelson, N., Photometric adaption of the Somogyi method for determination of glucose. J. Biol. Chem., 153:375-380, 1944.
18. Fiske, C. and Subbarow, Y., The colorimetric determination of phosphorus. J. Biol. Chem., 66:375-400, 1925.
19. Lozner, E. L., Winkler, H. W., Taylor, H. F. L. and Peters, J. P., Intravenous glucose tolerance test. J. Clin. Invest., 20: 507-515, 1941.
20. Cantarow, A. and Trumper, M., Clinical Biochemistry, Philadelphia, W. S. Saunders Co., p. 388, 1949.
21. Selye, H., Textbook of Clinical Endocrinology. Montreal, Acta Endocrinologica, p. 493, 1948.
22. Lazarow, A., Factors controlling the development and progression of diabetes. Phys. Rev., 29:48-74, 1949.
23. Himsworth, H. P., The syndrome of diabetes mellitus and its causes. Lancet, 1:465-473, 1949.
24. Bartelheimer, H., Die Regulation des Kohlehydrat stoffwechsels beim insulären und extrainsulären diabetes. Dtsch. Ztschr. F. Verdauungskrankh., 9:238-246, 272-284, 1949.
25. Young, F. G., Experimental observations on the course of diabetes. Proc. Roy. Soc. Med., 42:321-323, 1949.
26. Biskind, M. S. and Schreier, H., Significance of nutritional deficiency in diabetes. Exp. Med. and Surg., 3:299-316, 1945.
27. Collens, W. S., Slo-Bodkin, S. G., Rosenbliett, S. and Boas, L. C., Effect of estrogenic substance on human diabetes, J. A. M. A., 106:678-682, 1936.
28. Gschlacht, V., Ueber die Wirkung des Perandren bei Diabetes Mellitus, Schweiz. Med., Wchschr., 72:1-85, 1942.
29. Marcus, H. and Glotzer, S., Estrogens in diabetes, N. Y. State J. Med., 48:1461-1464, 1948.

MANAGEMENT OF BOWEL DYSFUNCTIONS IN CHILDREN

EDWARD E. P. SEIDMON, M. D., F. A. C. A., Plainfield, New Jersey

BOWEL DYSFUNCTION is a common complaint in children. Regardless of etiology, early diagnosis and treatment are of paramount importance for the future well-being of the child. Constipation or diarrhea left untreated in infancy and childhood may result in life-long disturbances much more difficult to handle in the adult.

Bockus (1) considers that constipation, a common complaint in adult life, frequently originates in early life. He states, "that in very early childhood, many children are trained to have bowel movements at a specified time—but too often they are not taught to answer the call to defecate, which may occur at other times during the day." He also attributes constipation in childhood to the fact that young children have to use adult toilet seats, where the posture is not ideal for normal defecation. Furthermore, the laxative abuse is begun in many households when the children are very young.

Bowel dysfunctions arise from a variety of causes—congenital, dietary, bacterial, environmental, allergic, etc. Congenital anomalies of the intestinal tract, such as megacolon, microcolon, diverticula, stenosis, etc., are frequently difficult to treat but fortunately, these conditions are comparatively rare. Bowel dysfunction of other origins are corrected with relative ease by standard procedures—changes in diet, avoidance of allergens, therapy aimed at eradication of specific bacterial invaders, etc.

Commonly occurring conditions in infants and children, such as constipation and diarrhea, are all too frequently treated by the mother as isolated episodes without regard to possible underlying causes and general disarrangement of normal bowel physiology. Irritant cathartics are frequently administered, setting up a pattern difficult to correct in later life. Treatment with harsh drugs is to be deprecated, although some medication is often indicated. (2)

EXPERIMENTAL

A group of 37 children was selected from an office practice restricted to pediatrics and allergy for a study of the pediatric applications of a hydrophilic colloid, methylcellulose, recommended by several investigators for the control of constipation, diarrhea and associated intestinal conditions. Methylcellulose is particularly suited for such uses since it is stated to be non-reactive, non-toxic, not degraded by gastrointestinal enzymes, and non-allergenic. (3) It was found to give good results in a large percentage of adult patients. (4, 5, 6, 7) No previous studies have been reported in the younger age group.

Some infants and young children in the series had been under care since birth and were known to have

TABLE I

CASES OF CHRONIC SIMPLE CONSTIPATION

Case No.	Age	Sex	Duration of Constipation	Dose of Methylcellulose, grams	Duration of Treatment	Adjuvant Therapy	Result	Remarks
3.	11 mo.	F	11 mo.	1.5	13 days	None	+++	Stools normal after 2 days. Remained normal since. Poor result previously with Neocultol and Vitamin B.
4.	2 yrs.	M	1 mo.	1.5	3 weeks		+++	Therapy unnecessary after 3 weeks.
7.	13 mo.	M	10 mo.	1.5	3 mo.		+++	Pellet stools. Constipation improved in 2 days. Methylcellulose discontinued after 3 months. No longer needed.
8.	9¾ yrs.	F	3-4 yrs.	1.5	5 mo.		+++	Excellent result with methylcellulose. Becomes constipated when discontinued.
9.	6 yrs.	F	2½ yrs.	1.5	1 mo.		++	Without medication, pellet stools at 2 to 6 day intervals.
12.	4 yrs.	F		1.5			0	Refused to take.
13.	3 yrs.	M	6 mo.	1.5	1 mo.	Petrogalar	+++	Anal fissures as result of constipation. Refused to sit on toilet. Petrogalar with methylcellulose for 3 weeks. Petrogalar discontinued. Good results with methylcellulose alone thereafter. Methylcellulose discontinued with good result.
14.	6½ yrs.	M		1.5	1 day		0	Constipation cleared with adequate diet alone. Refused methylcellulose medication.
15.	9 yrs.	F	1 yr.	1.5	1 mo.		+++	Complained of cramps—cramps disappeared with methylcellulose, normal bowel movement. Gained 1½ lbs. in 1 month.
16.	11 mo.	M	11 mo.	3	2 mo.		++	1.5 gm. helped but had cramps. 3 gm. methylcellulose stopped symptoms and cleared constipation.
24.	4½ yrs.	F	2 yrs.	1.5	6 weeks		+++	Methylcellulose produced daily normal movement. Occasional constipation with upper respiratory infection. Previously used Syntropan and Neocultol—condition improved but did not clear.
31.	2½ yrs.	F	1 yr.	3	2 weeks		+++	Frequency of urination cleared with correction of constipation.
33.	7½ yrs.	F	2 yrs.	3	3 weeks		+++	Previous to methylcellulose one hard stool daily. Now has normal movement.
34.	2½ yrs.	M	1 yr.	3	3 weeks		+++	Bowel movement every other day prior to methylcellulose. Normal after use of methylcellulose.
35.	1½ yrs.	M	4 mo.	2	3 weeks		+++	Intermittent constipation with hard stool prior to therapy.
37.	3 11/12 yrs.	F	9 mo.	3	3 weeks		++	Bowel movement every two days prior to medication of methylcellulose.

been constipated all their lives. In others, constipation was a more recent development. Prior to using methylcellulose, a standard prescription for constipation had been diet, Neocultol (R), various B-complex preparations and antispasmodics. Many of the children in the present series served as their own controls since their response to previous medication was known.

Patients in this study ranged in age from 7½ months to 13½ years with all but six patients being 6 years or under. They represented a variety of allergic and medical complaints but all required treatment for the correction of constipation.

A diagnosis was reached after a complete physical examination and appropriate laboratory studies. Where indicated, laboratory tests included blood studies, stool examination, complete skin testing, roentgen studies of the gastrointestinal tract, etc. Patients with gastrointestinal allergy were placed on elimination diets and all were started on ½ gm. methylcellulose t.i.d. in the form of Cellothyl (R*) tablets or granules. Where tablets were prescribed, mothers were instructed to crush them and sprinkle on cereal or fruit for young infants. Older children either chewed the tablets or swallowed them whole. The granules were administered by sprinkling on food. While adequate water intake has been stressed as essential for best results with methylcellulose in adults, no emphasis was placed on additional fluid intake in these infants and children. Sufficient medication was supplied for 30 days, unless the patient was to be seen at more frequent intervals.

*Cellothyl tablets and granules were supplied by Chilcott Laboratories, Division of The Maltine Company, Morris Plains, New Jersey.

RESULTS

The effectiveness of methylcellulose as a corrective for constipation was classified as follows:

+++ a normal soft stool daily.
++ a daily stool.
+ improved but constipation not corrected completely.
0 constipation not improved.

Of the 37 white patients, 3 children refused to take the medication after a few doses. In one case, symptoms were not improved; the 2 other children were aware that medication was being given and the parents did not insist that they continue. This problem was not encountered in the remaining 34 patients. In 26 patients, a+++ was observed; in 6, a++ and in 2, a+. There were no failures in the group who took the medication.

In Table I, observations are recorded on 16 children whose chief complaint was simple constipation. Fourteen responded well, 10 on a daily dose of 1.5

TABLE II

ALLERGIC CHILDREN WITH CONSTIPATION

Case Nos.	Age	Sex	Duration of Constipation	Dose of Methylcellulose, grams	Duration of Treatment	Previous Medication	Adjunctive Therapy	Diagnosis	Result	Remarks
1.	4 mo.	M		1.5	1 week			Colic G. I. allergy to milk.	0	Frothy stool, colic, relieved by Neocultol, Atropine. Methylcellulose caused more colic.
5.	3 yrs.	F	2 yrs.	1.5	4 weeks		Thyroid	Juvenile ricketts. G. I. allergy-mucous colitis	+++	Methylcellulose reduced to 1 gm. Constipation returned.
6.	4½ yrs.	M	4½ yrs.	1.5	6 mos.	Neostigmine bromide		G. I. allergy Pseudomegacolon.	++	Complete G. I. x-rays. Allergy skin tests. Diet elimination. Markedly allergic child.
10.	4 3/12 yrs.	M	4 3/12 yrs.	1.5	4 mos.	Neostigmine bromide (no result)	Neocultol	G. I. allergy Pseudomegacolon.	++	Methylcellulose reduced to 1 gm. No adjuvant therapy. Normal bowel movement.
11.	2 4/12 yrs.	M	2 4/12 yrs.	1.5	4 mos.	Amprotropine phosphate 66 mg. daily. Partial help.	None	G. I. allergy Pseudomegacolon.	+++	Constipated since birth. Pot belly. Methylcellulose alone after 3 mos. Less pot belly. Eats normal amount of food.
17.	13½ yrs.	F	10 yrs.	1.5	3 mos.		Desensitization diet.	G. I. allergy Cholecystitis Hay fever	+++	Methylcellulose, diet, desensitization resulted in normal daily bowel movement after 3 months.
18.	4 5/12 yrs.	M	3½ yrs.	1.5	3 mos.		Complete skin tests.	G. I. allergy Pseudomegacolon.	+++	Methylcellulose reduced size of stools.
20.	3 10/12 yrs.	F	3 yrs.	1.5	2 mos.			G. I. allergy Pseudomegacolon	+	Normal soft stools daily with methylcellulose.
21.	8½ yrs.	M	6-7 yrs.	1.5	2½ mos.		Complete skin test	G. I. and upper respiratory allergy. Asthma. Migraine.	+++	Normal stool within 7 days. No asthma after correction of constipation. Headaches cleared.
22.	7½ mos.	M	5 mos	1.5	2 mos.		Elimination diet	Eczema	+	Soft stool.
23.	5 4/12 yrs.	F	5 mos.	1.5	6 weeks			Atopic eczema. Occ. diarrhea	+++	
26	2 4/12 yrs	F	1½ yrs.	3	6 weeks		Elimination diet	Atopic eczema Asthma	+++	Asthma cleared completely with correction of constipation.
27	9 9/12 yrs	M	9 yrs.	1.5	7 mos.			Hay fever	+++	After 3 gm. for 2 mos. had normal daily bowel movement. Constipated intermittently all his life.
30.	7 2/12 yrs.	F	7 2/12 yrs.	3	1 mo.			Urticaria	+++	Urticaria cleared when constipation was corrected.
29.	4½ yrs.	F	1 yr.	3	1 mo.	Milk of Magnesia. Temp. relief	Elimination diet	Chronic urticaria	+++	Clearing of constipation cleared urticaria.
32.	3½ mos.	F	3 mos.	1	4 weeks			G. I. allergy	+++	Constipated—hard marble stool. Now normal bowel movement.
36.	2 yrs.	M	13 mos.	3	3 weeks			G. I. allergy	+++	Hard marble type stool daily before medication.

gm. per day, while 6 required 2 to 3 gms. daily before an effective response was noted.

Table II presents results obtained in 17 other children with a variety of complaints; all, however, had allergic manifestations. It is interesting to note that adequate diet and clearing of constipation appeared to relieve rapidly asthma in two cases and urticaria in two others.

In addition to allergy, 5 children in this series had constipation as a complaint probably due to pseudomegacolon. (8) These children did not show true congenital megacolon but had the following symptoms: pot belly, constipation and adult-sized stools, apparently due to increased calibre of the colon. Two other children with similar manifestations but without allergic reactions are also included in Table III.

The following case history described a typical patient of this group:

CASE NO. 6—W.T.

Presenting Complaint:—The patient was first seen at 16 months of age with a presenting complaint of constipation with pebble-like stools, difficulty in sleeping, restlessness,

atopic eczema on chest and arms and colicky pains in the abdomen following ingestion of cow's milk.

Past History:—Child had been on breast feeding for three weeks following birth and developed a rash on chest and arms. He was then changed to cow's milk when he started to cry after each feeding, continuing to cry up to the next feeding. He had had excess mucous in the stools from three weeks of age to sixteen months.

Physical Examination:—Physical examination revealed a very restless, white male child, weight 25 pounds, 3 ounces; 32'' tall. Eye, ear, nose and throat, heart and lungs were essentially negative. The abdomen was markedly distended with a pot belly. Bilateral atopic eczema was observed on the chest and the anticubital fossae. Fluoroscopic examination of the abdomen revealed marked distention of the stomach and bowel, three wrist bones present.

Laboratory Tests:—Hemoglobin 84%; red blood cells 4 million; smear of the bowel showed numerous mucous flakes and many eosinophils. Passive transfer protein skin sensitization tests revealed positive results to cow's milk, fish, tomato, lima bean, orange, spinach, banana, chocolate, wheat, white potato and egg.

X-rays:—X-ray of the gastrointestinal tract taken at 18 months showed pylorospasm, spasm of the duodenum, slow emptying time of the stomach; the large bowel was hyperactive with stasis in the sigmoid colon and rectum.

Treatment:—The patient was placed on a diet of Amigen (R) feedings and synthetic vitamins A, B, C, and D. Later foods gradually introduced included rye, oat, beef, veal, gelatin, carrots, spinach, squash and prunes. The diet was fat free, substituting soy bean oil for fat. At 18 months, he was placed on the Petrogalar (R) and neostigmine bromide. Petrogalar (R) partially relieved his constipation, his appetite began to improve and the pot belly decreased in size but he was still constipated intermittently. This treatment was continued with only moderate success. At the age of 4 3/4 years, Petrogalar (R) was stopped and methylcellulose 0.5 grams t. i. d. was prescribed. Stools became normal in size and of daily occurrence instead of pebble-like every other day. Neostigmine 7.5 mgs. was continued. When neostigmine was stopped, constipation returned. When methylcellulose was stopped, constipation also returned. When both were given together, constipation was controlled. With the diet elimination, atopic eczema disappeared.

In Table III are listed the cases not otherwise classified. Bargen (5) has reported methylcellulose helpful in irritable bowel syndrome in adults. Two children with this condition (Cases Nos. 19 and 28 with diarrhea and abdominal cramps) were benefited by the addition of methylcellulose to their regimen.

DISCUSSION

It is often possible to correct bowel dysfunction in children by dietary means alone. However, every pediatrician has need for drug therapy and laxatives in some cases. Many laxatives, including the natural gums such as tragacanth, karaya, arabic, (8, 9) are known to be allergenic and therefore should be avoided, particularly in allergic children. Methylcellulose seems to fill the need for a physiologic type bulk producer, free from allergenic properties. It appeared to produce better results than medication previously used. While the tablets have obvious advantages for older children and adults, the granular type was easier to administer to the younger children.

It was particularly noteworthy during this study that all patients gained weight at a faster rate than previously. It is interesting to speculate as to whether such a gain reflects merely an improved sense of well-being or whether there was an actual improvement in the functional "efficiency" of the intestinal tract and better absorption of nutritive materials as a result.

From a physiologic standpoint, absorption of substances from the colon is restricted mainly to water and inorganic salts. Glucose solutions may be absorbed in considerable amounts, but proteins and fats are not absorbed. (11) From the pharmacologic standpoint, many soluble substances (drugs) may be absorbed from the rectum and colon, and the effects are often greater or more prompt than with oral administration. (12) Nevertheless, conclusive evidence is lacking that toxic substances formed in the colon are absorbed in sufficient amounts to produce systemic effects. It is believed that toxic substances formed, by the decomposition of protein by the normal bacterial flora-indole, skatole, histamine, etc., are prevented from entering the systemic circulation by the bowel wall barrier, and through the detoxicating action of the liver. (11, 13)

In view of much of the evidence, it is difficult to explain the systemic effects of constipation—headache, furred tongue, malaise—as resulting from absorption of toxic substances from the larger intestine. One ex-

TABLE III

MISCELLANEOUS

Case No.	Age	Sex	Duration of Constipation	Dose of Methylcellulose, grams	Duration of Treatment	Adjuvant Therapy	Diagnosis	Result	Remarks
2.	2 yrs.	M	2 yrs.	1.5	2 mos	Diet	Pseudo-megacolon	+++	Therapy unnecessary after 3 months.
19.	2½ yrs.	F	6 wks.	1.5	1 mo.	Diet	Diarrhea Abdominal pain, acholic stool	++	Methylcellulose cleared loose stools. Stools now normal.
25.	5½ yrs.	F	3 mos.	3	6 weeks	Diet	Pseudo-megacolon Constipation	++	Requiring enemas. Pellet stools. 1.5 gm. daily inadequate.
28.	20 mos.	F	2½ mos.	3	2½ mos	Diet	Diarrhea with Colitis	++	Methylcellulose checked diarrhea. Had formed stools.

planation is that the mechanism is reflex in action rather than toxic, probably due to small waves of contraction originating in the wall of the loaded bowel, travelling in a reverse direction over the small intestine, stomach and esophagus. (14)

Much is still unknown, however, concerning the actual degree of absorption from the colon. In experimental animals, it has been shown that non-pathogenic bacteria (15) and yeast (16) pass through the colonic mucosa and may be isolated from the abdominal organs and mesenteric lymph nodes. It is generally believed that the natural bacterial flora of the large intestine remains within the lumen under normal conditions. Nevertheless, it is now shown that E. coli tagged with radiocative iodine migrate into the peritoneal cavity when the serosa is irritated. (17) It has also been shown that allergens may be absorbed from the rectum as rapidly as when given by mouth (18). It seems justifiable to conclude that in certain instances, bacteria, allergens, and possibly toxic substances may be absorbed from the colon.

Correction of colonic dysfunction in children using methylcellulose as an adjunct to general management, is believed to be of considerable importance for the maintenance of general well-being. This is particularly true in the younger age groups.

SUMMARY

1. In a series of 37 pediatric patients with bowel dysfunction, including constipation, diarrhea, and irritable bowel syndrome, methylcellulose was a helpful adjunct to general management.

2. A good response was obtained in 34 of the 37 cases and in most instances, it was possible to discontinue medication after a reasonable period without recurrence.

3. Patients with pseudomegacolon, who had previously obtained poor results with antispasmodics, were benefited by methylcellulose.

4. Although 17 children in the series had allergic manifestations, no allergic symptoms due to methylcellulose (Cellothyl) developed in any of the patients during treatment. On the contrary, in 2 children with asthma and 2 with urticaria, the correction of their constipation was followed by relief of the allergy.

REFERENCES

1. Bockus, H. L.: Gastroenterology, Vol. II, W. B. Saunders, Philadelphia, Pa., 1943. Pages 510-511.
2. Mitchell-Nelson: Textbook of Pediatrics, W. B. Saunders, Philadelphia, Pa., 5th Ed. 1950. Page 808.
3. Editorial, J. A. M. A. 127:922 (Apr. 14) 1945.
4. Schweig, Karl: The Use of Methylcellulose as a Bulk Laxative; New York State J. of Med. 48:1822-1823 (Aug. 15) 1948.
5. Bargen, J. A.: A Method of Improving Function of the Bowel: The Use of Methylcellulose; Gastroenterology 13: 275 (Oct.) 1949.
6. Goetzel, Franz R. and Newey, James A.: Methyl Cellulose Therapy in Chronic Constipation; Permanente Found. M. Bull. 7:67-78 (July) 1949.
7. Musick, Vern. H.: Effectiveness of Methylcellulose in Gastrointestinal Disturbances: J. Oklahoma M. A. 43:360-364, (August) 1950.
8. Hirschman, L. J.: Some Common Proctologic Conditions of Childhood; J. South Carolina M. A. 42:267-272 (Oct.) 1946.
9. Gelfand, H. Harold: The Vegetable Gums by Ingestion in the Etiology of Allergic Disorders; J. Allergy 20:311-321 (Sept.) 1949.
10. Feinberg, Samuel A. and Schoenkerman, Bert B.: Karaya and Related Gums as Causes of Atopy; Wisconsin M. J. 39:734-736, 1940.
11. Best, Charles H. and Taylor, Norman B.: The Physiological Basis of Medical Practice; The Williams & Wilkins Company, Baltimore, Maryland, 4th Ed. 1945. Page 504, 508.
12. Solimann, T.: Manual of Pharmacology, W. B. Sanders Co., Philadelphia, Pa., 7th Ed. Page 26.
13. Seidmon, E. E. P., and Arnold, L.: Influence of Vitamin A and B Deficiency upon Intestinal Acid-base Equilibrium and Bacterial Flora; Proc. Soc. Exp. Biol. and Med. 29: 488-490, 1932.
14. Alvarez, Walter C.: An Introduction to Gastroenterology, Paul B. Hoeber Inc., New York, 3rd Impression, 1939. Page 553.
15. Shugar, M. and Arnold, L.: Absorption of Bacteria from the Large Intestine: Proc. Soc. Exp. Biol. and Med. 29:494-496, 1932.
16. Fisher, V.: Absorption of Yeast from the Large Intestine: Proc. Soc. Exp. Biol. and Med. 29:490-494, 1932.
17. Schweinburg, F. B., Seligman, A. M. and Fine, J.: Transmural Migration of Intestinal Bacteria; New England J. Med. 242:747-751 (May 11) 1950.
18. Gray, I., and Walzer, M.: Studies in Absorption of Undigested Protein in Human Beings. VIII Absorption from the Rectum and a Comparative Study of Absorption Following Oral, Duodenal and Rectal Administration; J. Allergy 11:245-250, 1940.

THE EFFECT OF MINERAL OIL ON FOOD UTILIZATION
II. CHANGES OF BETA-CAROTENE IN MINERAL OIL

MARY F. PAUL, VICTOR R. ELLS, AND HENRY E. PAUL Norwich, N. Y.

THE deleterious effect of mineral oil upon the utilization of fat-soluble vitamins has been frequently demonstrated (1, 2, 3, 4). That this effect is greater on carotene than on vitamin A itself has also been recognized. The hypothesis has been advanced (3) that mineral oil, being a hydrocarbon, possesses a greater solvent power for the hydrocarbon carotene than is possessed by the lipids of the intestinal fluids, thereby preventing intestinal absorption of carotene.

Vitamin A has been considered to be preferentially dissolved by the lipids of the digestive tract and thereby a considerable portion removed from the mineral oil (3).

In addition to the effect of mineral oil on carotene and vitamin A utilization, various workers, (5, 6)

Submitted March 13, 1951.

(From the Division of Biology, Eaton Laboratories, Inc. Norwich, N. Y.)

have reported serious interference with vitamin D utilization in animals receiving mineral oil. Since vitamin D is considered to have a sterol structure, the explanation of preferential hydrocarbon solubility did not seem adequate in this case.

In an investigation in this laboratory using the U.S.P. XIII vitamin A test diet, it was again observed that concurrent feeding of mineral oil markedly lowered the utilization of carotene from carrots by albino rats. However, by increasing the amount of carrots fed from 100 mg. to 200 mg. per rat daily, growth could be restored even in the presence of mineral oil (Table I). Since the solubility of carotene in mineral oil was not exceeded by this increase (1), the possibility of an equilibrium type of chemical change as well as preferential solubility of the carotene in mineral oil is suggested as a partial explanation of the deleterious effect of mineral oil on carotene utilization.

Several workers have studied the various stereo-isomers of *trans*-beta-carotene and noted differences in biological activity. Kemmerer and Fraps (8) reported that neo-beta-carotene B had about one-half the activity of all-*trans*-beta-carotene. Deuel et al. (9) reported that neo-beta-carotene U had about 38% of the biological activity of all-*trans*-beta-carotene. Kemmerer and Fraps (10) reported neo-beta carotene U to have about 25% of the activity of all-*trans*-beta-carotene, and ascribed the biological activity to steric rearrangement within the intestinal tract of about 25% of the neo-beta-carotene U to *trans*-beta-carotene.

Various stereo-isomers may be formed by boiling beta-carotene in hexane (11) or by iodine catalysis in hexane (12). The relationship of hexane to mineral oil suggested that a similar reaction might take place in mineral oil under suitable conditions. The following investigation was undertaken to determine the possibility of stereo-isomerization of beta-carotene in the presence of mineral oil.

TABLE I

Effect of Mineral Oil Upon the Utilization of Carotene From Carrots as a Source of Vitamin A

No. Animals	Amt. Carrots per rat per day	Mineral Oil per rat per day	Ave. gain 4 wks. gm.
12	100 mg.	none	44.8
12	100 mg.	0.2 ml.	14.6
11	200 mg.	0.2 ml.	41.3

EXPERIMENTAL

Pure *trans*-beta-carotene (*2*) was dissolved in light mineral oil (liquid petrolatum, USP XIII) to give a concentration of 40-50 mg. per liter. These solutions were diluted 2:25 with solvent (hexane, Eastman Pract.; or Skellysolve B; both redistilled) for the spectrophotometric readings. Because of the difficulty of dissolving a given amount of carotene in mineral oil within a reasonable time, the solutions were prepared by adding a considerable excess of beta-carotene to the mineral oil and shaking frequently over a period of several hours. The excess carotene was then removed by centrifugation, the concentration determined spectrophotometrically, and dilution to the desired concentration made with mineral oil. Samples

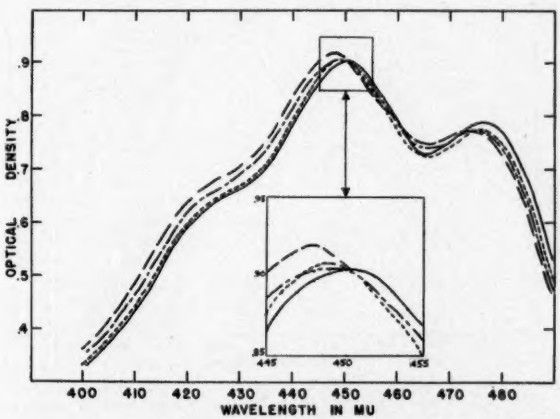


Fig. 1—Spectral absorption characteristics of solutions of beta-carotene in mineral oil—*in vitro* incubation.

———— (1) Original solution of beta-carotene in mineral oil. Identical curve obtained on refrigerated (10° C) solution.

– – – – – (2) Portion of (1) after 4 weeks' storage at room temperature (25-28° C).

—— – – —— (3) Portion of (1) after 2 weeks' storage at 37° C.

—— —— (4) Portion of (1) after 5 weeks' storage at 37° C.

The original carotene concentration was 50 mg. per liter. This solution was diluted 2 ml. → 25 ml. for the spectrophotometric determinations. For convenience in comparison, all curves were calculated to the same density at 450 mu by multiplying the observed densities by a factor. The factors used were (1) 1.00 (2) 1.03 (3) 1.074 (4) 1.16.

of the mineral oil solution of beta-carotene thus prepared were stored at 10° C, at 25-30° C and at 37° C. A portion was also used for *in vivo* experiments on albino rats.

The concentrations of total carotene were determined from the absorption at 436 mu by the method of Beadle and Zscheile (13), where all-*trans*-beta-carotene and neo-beta-carotene U have the same absorption (specific absorption=196), and the concentration of *trans*-beta-carotene from the reading at 436 mu and that at 478 mu. Pure *trans*-beta-carotene has its absorption maxima at 450 mu and at 477-478 mu. When some of the beta-carotene is changed to isomeric forms, the maxima shift to shorter wavelengths. The maxima of pure neo-beta-carotene U in hexane (14) are at 446-447 mu and at 474 mu. The maxima of neo-beta-carotene B in hexane (13) are at 442.5 and 467 mu. About a dozen isomers of beta-carotene have been observed (12) in the chromatographic column under suitable conditions.

The absorption curve of the beta-carotene dissolved in mineral oil was determined immediately using the Beckman spectrophotometer. Determinations of the spectral absorption of the samples stored at 10° C, at room temperature (25-30° C) and at 37° C were made at intervals. Representative curves appear in Figure 1. It may be seen that a shift has occurred in the absorption peaks suggestive of the formation of stereo-isomers. In the refrigerated samples, no change occurred over a period of several weeks. At room temperature, the change took place quite slowly reaching equilibrium in 4-5 weeks. At 37° C equilibrium was attained in a somewhat shorter time, with a larger proportion of the neo form present (cf. Fig. 1). The maxima were shifted from 450 mu to 448-449 mu and from 476 to 473-475 mu during this change. Some of these solutions were also investigated chromatographically (see below). The changes under these *in vitro* conditions were considered of sufficient magnitude to warrant investigation of changes which might occur under *in vivo* conditions.

Young rats which had been depleted of their vitamin A stores on the U.S.P. XIII vitamin A test diet (about 4-5 weeks on diet) were assembled into two groups of 5 animals each. One group served as controls and received 1 ml. of mineral oil per rat per day by mouth. The other group received 1 ml. per rat of the fresh solution of *trans*-beta-carotene in mineral oil (50 mg. per liter). These materials were administered daily for three days and the animals killed on the fourth day. The abdominal cavities were opened and when the intestines were exposed to view, pools of mineral oil could be seen throughout the intestinal tract. Samples of the mineral oil were removed from the caecum and large intestine by puncturing the wall with a hypodermic needle and withdrawing the oil into a syringe. The samples from the five rats were composited for each group. The samples were centri-

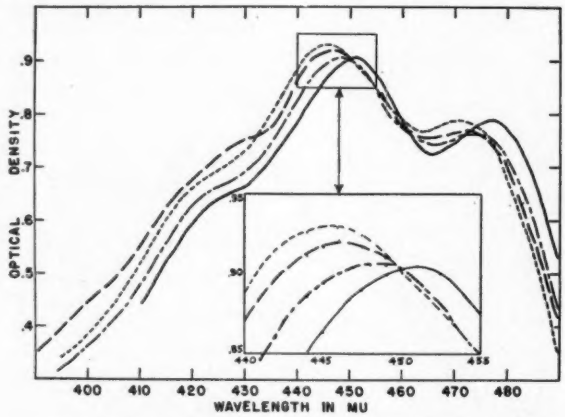


Fig. 2—Spectral absorption characteristics of beta-carotene in mineral oil—*in vitro* studies. Chromatographic fractionation of carotene isomers.

———— (1) Original solution of beta-carotene in mineral oil.

—— —— (2) Carotene in mineral oil as obtained from the rat intestine.

—— – —— (3) Lower yellow band obtained by chromatographic treatment of (2) on $Mg(OH)_2$ column.

– – – – – (4) Upper yellow band obtained by chromatographic treatment of (2) on $Mg(OH)_2$ column.

The original carotene concentration was 50 mg. per liter. This solution and the oil recovered from the intestinal tract were diluted 2 ml → 25 ml. for the spectrophotometric determinations. For convenience in comparison, all curves were calculated to the same density at 450 mu by multiplying the observed densities by a factor. The factors used were (1) 1.00 (2) 1.818. The observations on the chromatographic fractions were made for qualitative changes with no attempt to measure quantitative changes.

fuged in a microcentrifuge and the clear layer of oil used for spectrophotometric analysis. The sample from the control group served as a blank to compensate for interfering materials from the intestinal tract which might have dissolved in the mineral oil.

This experiment was repeated twice using animals which had been on the U.S.P. vitamin A test diet for 2 weeks. According to Kemmerer and Fraps (15), maintenance for 3 days on the U.S.P. test diet is sufficient to remove all but traces of carotene from the digestive tract. The animals were divided into 2 groups of six each. They were dosed for 3 days as in the previous experiment and killed on the fourth day. Since these animals were not entirely depleted they were in a much better nutritional state than the animals of the first experiment. In this later experiment there was more food in the intestinal tract and the oil did not tend to collect in large pools but in small drops. Since these small drops could not be withdrawn by syringe, the intestinal tract beginning with the caecum and extending to the anus was removed and the contents extruded into 50 ml. centrifuge tubes. The material was composited for each group, water added, and centrifuged. The mineral oil layer rose to the top and was removed and further centrifuged in a micro-centrifuge. The clear oil obtained was submitted to spectrophotometric and chromatographic treatment.

The presence of the mineral oil resulted in slow and uneven passage of the material through chromatographic columns with discoloration and poor definition of the bands, in the case of most column materials tested. Several brands of calcium hydroxide, and magnesium oxide and hydroxide with and without added Hyflo Supercel, as well as alumina (Merck, according to Brockmann) were tried. Magnesium hydroxide (Medicinal Powder, Baker) was found to be the most satisfactory and a reasonable rate of flow and good band definition resulted.

The oil obtained from the intestinal tracts of the rats was diluted with a 1:1 hexane-Skellysolve B mixture and placed on the $Mg(OH)_2$ column. Two bands were formed and collected separately by the flowing chromatogram technique. A very faint narrow yellow band preceded these two down the column, but contained insufficient material for investigation.

Results typical of the three experiments may be seen in Fig. 2. The spectral characteristics of the untreated oil recovered from the rats (curve 2, Fig. 2) compared with pure carotene indicate that a shift in the absorption maxima towards shorter wavelengths has occurred. The spectral characteristics of the bands obtained from the chromatographic column reveal separation into two carotene fractions. The characteristics of the lower band (curve 3, Fig. 2) are more similar to those of *trans*-beta-carotene and may indicate another stereo-isomer or incomplete separation of *trans*-beta-carotene from one of its stereo-isomers. No further purification was attempted. The characteristics of the upper band (curve 4, Fig. 2) are markedly similar to those of neo-beta-carotene U as described by Polgar and Zechmeister (12) and Zechmeister and Polgar (14).

A sample of the carotene in mineral oil kept at 37° C for 5 weeks was subjected to similar chromatographic treatment. Fractions having the same absorption maxima were obtained as in the *in vitro* experiment, there being relatively less of the 445 mu absorbing fraction in the *in vitro* sample.

An *in vitro* experiment substituting Wesson oil for mineral oil was also carried out at 37° C. There was no appreciable shift in the absorption maxima of beta-carotene for the first two weeks, but after 3 to 4 weeks there was a slight shift of approximately the same amount as that occurring in mineral oil in 1 to 2 days.

DISCUSSION

The results of the *in vitro* experiments on the incubation of beta-carotene in mineral oil are similar to those obtained by Zechmeister and Tuzson (11) in hexane and indicate the formation of isomers of beta-carotene. The feeding experiments indicate that a similar and more rapid conversion of *trans*-beta-carotene occurs in the digestive tract of the albino rat in the presence of mineral oil. Since the isomers of *trans*-beta-carotene which have been studied to date (8, 9) have been shown to have lowered biological activity, it is believed that this conversion may contribute to the lowered utilization of carotene when administered with mineral oil.

It has frequently been reported (3) that the utilization of vitamin A is less affected by mineral oil than is carotene. A stereo-isomer of vitamin A has been formed (16) by iodine catalysis. The biological activity of the stereo-isomer was equivalent to that of the vitamin A from which it was formed. Occurrence of stereoisomerization of vitamin A in mineral oil would not necessarily, therefore, adversely affect the utilization of vitamin A. The lower biological activity of the stereoisomers of carotene and the retention of biological activity by the stereo-isomer of vitamin A might partially explain the difference in the effect of mineral oil on carotene and on vitamin A utilization. Vitamin D utilization has been shown to be adversely affected by mineral oil ingestion (6). Since stereo-isomers of provitamin D which cannot be converted to biologically active material have been described (17), the possibility of the formation of isomers of vitamin D in mineral oil-fed rats should be considered.

CONCLUSION

On the basis of the experiments reported here, stereoisomerization of beta-carotene is believed to occur both *in vitro* and *in vivo* in the presense of mineral oil. The lower biological activity of the stereo-isomers may account in part for the deleterious action of mineral oil on carotene utilization.

REFERENCES

1. Burrows, M. T., and Farr, W. K., Proc. Soc. Exptl. Biol. Med. *24*, 719 (1927).
2. Jackson, R. W., J. Nutrition *4*, 171 (1931).
3. Dutcher, R. A., Harris, P. L., Hartzler, E. R., and Guerrant, N. B., J. Nutrition *8*, 269 (1934).
4. Curtis, A. C., and Ballmer, R. S., J. Am. Med. Assoc. *113*, 1785 (1939).
5. Jackson, R. W., J. Nutrition *7*, 617 (1934).
6. Smith, Margaret Cammark, and Spector, Harry, Univ. Ariz. Ag. Expt. Sta., Tech. Bull. *84*, 373 (1940).

7. Hawk, P. B. Oser, B. L., and Summerson, W. H., Practical Physiological Chemistry, Blakiston, Philadelphia, p. 1243 (1947).
8. Kemmerer, A. R., and Fraps, G. S., Ind. Eng. Chem. *15*, 714 (1943).
9. Deuel, Harry, J., Jr., Johnston, Cornelia, Sumner, Elizabeth, Polgar, A., and Zechmeister, L., Arch. Biochm. 5, 107 (1944).
10. Kemmerer, A. R, and Fraps, G. S., J. Biol. Chem. *161*, 305 (1945).
11. Zechmeister, L., and Tuzson, P., Biochem. J. *32*, 1305 (1938).
12. Polgar, A. and Zechmeister, L., J. Am. Chem. Soc. *64*, 1856 (1942).
13. Beadle, B. W., and Zscheile, F. P., J. Biol. Chem. *144*, 21 1942).
14. Zechmeister, L. and Polgar, A., J, Am. Chem. Soc., *65*, 1522 (1943).
15. Kemmerer, A. R., and Fraps, G. S., J. Nutrition *16*, 309 (1938).
16. Robeson, C. D. and Baxter, J. G., Nature *155*, 300 (1945).
17. Rosenberg, H. R., Chemistry and Physiology of the Vitamins, Interscience, New York, p. 399 (1942).

LYSOZYME ACTIVITY IN GASTRIC JUICE OF NORMAL ADULTS: PRELIMINARY REPORT.

OTTO E. LOBSTEIN and SAMUEL J. FOGELSON, Chicago, Illinois

IT WAS suggested by Prudden, Lane, and Meyer (1) that lysozyme can be regarded as a causative factor in alimentary ulcerative disease. We analysed the gastric juice of 13 normal subjects (medical students) with respect to lytic activity of lysozyme. The present report states the amount of lysozyme we found in the residuum of the fasting morning gastric juice.

The method we have employed was that of Hartsell and Smolelis (2), modified by us (3), which we found to be accurate, rapid, reproducible, and applicable to a large number of samples.

The results are tabulated in table No. 1, and show a range of 2.6 to 19.2 micrograms lysozyme per ml gastric juice with a mean of 7.57 ± 4.6 (61%).

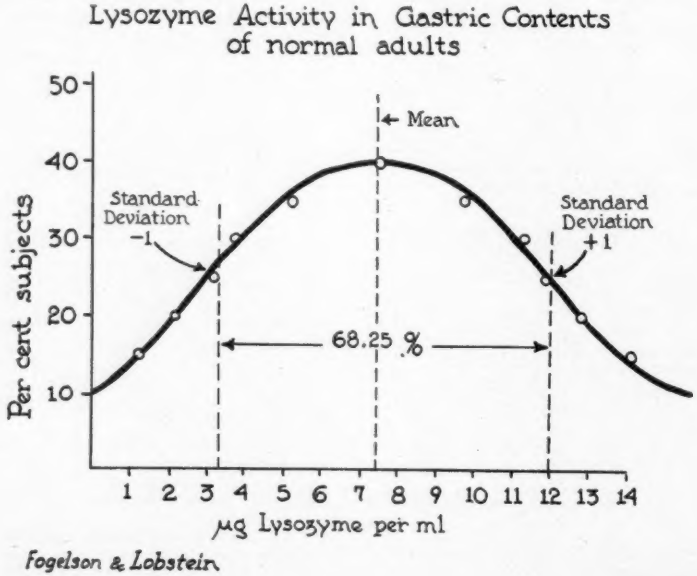
Submitted March 30, 1951.

From the Department of Chemistry and Surgery, The Medical School of Northwestern University, Chicago, Illinois.

TABLE 1.

No.	Subject	sex	micrograms lysozyme per ml gastric contents
1	R.K.	m	4.6
2	L.P.	m	2.5
3	E.S.	m	2.6
4	L.M.	m	10.9
5	G.R.	m	7.0
6	R.M.	m	11.6
7	C.R.	m	6.1
8	J.P.	f	6.8
9	M.P.	f	19.2
10	V.K.	f	8.7
11	J.G.	m	2.3
12	J.N.	m	6.9
13	B.H.	f	9.2

mean: 7.57 ± 4.6 (61%)



The 95% confidence limit (95 out of 100 times the range would be) was calculated to be 4.7 to 10.4 micrograms lysozyme per ml gastric juice, and the 99% confidence limit is 3.6 to 11.5 micrograms lysozyme per ml gastric juice.

TABLE 2

The normal distribution curve was plotted using the values tabulated in table 2:

Standard deviation	Lysozyme deviation	mean less deviation	mean plus deviation	percent of subjects
0.00	0.00	7.57	7.57	40
0.51	2.35	5.22	9.92	35
0.84	3.86	3.71	11.43	30
0.96	4.42	3.15	11.99	25
1.17	5.38	2.19	12.95	20
1.40	6.44	1.13	14.01	15

The normal distribution curve is shown in fig. 1 with ± 1 standard deviation representing 68.3% of the total area. The standard error is 1.28 which is rather high indicating that chances are less than 68 in 100 that there is no sampling error.

REFERENCES

1. Prudden J. F., Lane N., Meyer K. Am. J. of the Med. Sciences, *219*, 291-300, March, 1950.
2. Hartsell S. E., Somlelis A. N. J. Bact., *58*, No. 6, Dec. 1949.
3. Lobstein, O. E., Fogelson S. J., Quart. Bull. Northwestern Univ. Med. School, *25* (2) 89. Summer 1951.

THE USE OF ADENOSINE-5-MONO PHOSPHATE IN THE PRURITUS OF OBSTRUCTIVE JAUNDICE

LOUIS PELNER, M.D., F.A.C.A. and SAMUEL WALDMAN, M.D., F.A.C.P., Brooklyn, N. Y.

THIS NOTE concerns the salutary effects of adenosine-5-mono phosphate (A5MP) on the pruritus of obstructive jaundice, a condition for which there has been no satisfactory therapy in the past. In a recent article on the management of jaundice, Steigmann (1) stated that pruritus is encountered most often in surgical jaundice and it is frequently one of the complaints with which it is most difficult to deal. Of course, proper surgical therapy alleviates this symptom, but a delay of 5 to 7 days or longer usually occurs before the exact diagnosis can be made. Occasionally pruritus is so severe, that even suicide is threatened. According to a survey, quoted by Movitt (2), from Mever and Steigmann, pruritus is present in 41% of malignant obstructive jaundice and in 21% of benign obstructive jaundice.

Weiss (3) lists the following medications for the treatment of pruritus of obstructive jaundice, none of which have proved satisfactory in our hands: gynergen, orally or intravenously, baths with oatmeal, corn starch or bicarbonate of soda, dusting powders containing menthol or anesthesin, and lotions containing phenol and calamine or diluted vinegar. Steigmann (1) adds that the antihistaminics have not proved to be of value, but that intravenuous procaine hydrochloride in 0.1% or 0.2% solution has offered striking relief to some patients. This is undoubtedly true, but the personal knowledge of several severe reactions and near fatalities from this solution, makes its use hazardous and also unnecessary, especially if a less troublesome medicament will give the same results.

A5MP is an essential metabolite, and is intimately associated with basic life processes. It is present in coenzymes I and II and flavin dinucleotides and is one of the fundamental substances in phosphorylation reactions. It is one of the compounds involved in the reactions that store energy and subsequently make it available in metabolic processes. In addition, it is also important in carbohydrate and fat metabolism.

The exact dosage of this medicament has not been arrived at yet, nor is its method of action exactly known. Our theory of its action will be discussed subsequently. The dosage that we used for treatment in our patients was 1 ampoule (20 mg.) intramuscularly three times daily. A new dosage form, now available, which gives a sustained action, contains 20 mg. of A5MP in 1 c.c. of gelatin. This should reduce the required dosage to 1 cc. daily.

CASE I

J. B., female, age 55, came with a complaint of severe, incessant pruritus of six days duration. This did not yield to any of the usual measures including bicarbonate baths and locally applied calamine lotion with phenol. The patient was obviously deeply jaundiced, yet at this visit she complained only of the pruritus. She gave a history that twenty years ago she had her first gall bladder attack. She was placed on a low fat diet for one year, and thereafter disregarded this precaution because she enjoyed good health. Six weeks prior to the onset of the pruritus, pain had recurred in the right upper quadrant of the abdomen; this pain radiated to the left upper quadrant and to the back. The pain was associated with vomiting and was aggravated by food. A cholecystogram taken a week later revealed an absence of filling of the gall bladder. She was placed on a low fat, soft diet with antispasmodics, and did rather well for several weeks. One week prior to the onset of pruritus, the pain and vomiting recurred but remained only a very short time. A week later she was suddenly awakened with intense itching, which interfered with her sleep and which continued unabated for six days, so that she finally presented herself for this complaint. She had no pain in her abdomen, and no nausea or vomiting. She also stated that her stools were of natural brown color. She gave a history of weight loss of 21 lbs. in six weeks, which she attributed to lessened food intake.

The presumptive diagnosis was jaundice due to a calculus partially obstructing the common bile duct, and she was hospitalized for further work-up and treatment.

The physical examination revealed a patient with scleral and cutaneous icterus. There were many scratch marks and erythematous areas. The pulse was 60, the respirations were 18 and blood pressure was 120/70. There were no spiders or liver

Submitted March 8, 1951.

palms. The heart showed no remarkable findings. There was right upper quadrant tenderness in the abdomen, and jar tenderness over the right lower ribs.

The laboratory findings were as follows: the specific gravity of the urine was 1.010 and it was positive for bile and for urobilinogen. A laboratory study of the blood revealed the following: Hgb.-14 gms., red blood count 4,270,000, white blood count—6,400 with 71% polymorphonuclear cells. The fasting blood sugar was 60 mgs. and the urea nitrogen was 14 mgs. per 100 cc. The total proteins were 7.3 gms. with an albumin of 3.8 gms. and a globulin value of 3.5 gms. per 100 cc. The alkaline phosphatase was 22.8 units. The icterus index was 77.6 units. A van den Bergh test revealed a direct value of 2.7, an indirect value of 3.9, and a total of 6.6 mgs. The cephalin flocculation test was negative, and the thymol turbidity test was 5 units. The Wassermann was negative and the prothrombin time was 19 seconds with a control of 16 seconds. The diagnosis of a partial obstruction seemed confirmed.

Since it took about five days for the work-up to be completed at the hospital, the itching of this patient had to be relieved, because this was her major and only actual complaint. An ampoule of A5MP (20 mgs.) was given three times a day. After the first injection the patient remained symptom-free until she was operated upon. A gall bladder full of calculi was removed, as well as several calculi which were obstructing the common bile duct. A T-tube was inserted into the common bile duct, and later removed after a cholangiogram revealed the duct to be completely patent. There was no further itching at any time.

CASE II

H. A. S., a 35 year old married female was delivered of a full term female child in July 1950. On September 23, she complained of some upper abdominal distress, some right upper quadrant pain and nausea a few days after a mild upper respiratory infection. Vomiting occurred spontaneously on one occasion and was self-induced on two occasions with relief. Nausea, belching and fullness were prominent symptoms after meals. Fatigue was present. Mid epigastric tenderness was noted at that time. About one week later, the patient noted that her urine was dark and that her stools were light colored. Generalized pruritus developed causing marked discomfort and incessant scratching. A marked sense of weakness was prominent. Calamine lotion and Caladryl lotion (a combination of Calamine and Benadryl) were used with little effect. Two days later it was noted that the patient was jaundiced. There was no previous history of hepatic or biliary tract disease. No hepatotoxic drugs had been ingested and no plasma or transfusions had been administered in the preceding few months.

The only pertinent findings on examination were cutaneous and mucosal jaundice, and tenderness in the right upper quadrant with a smooth liver edge palpable two finger breadths below the right costal margin. The gall bladder was not palpable. No lymphadenopathy or splenomegaly was noted. The stools were light colored and the urine contained bile.

The laboratory data during the patient's 16 day hospital stay are noted in Table I. A complete gastro-intestinal series was negative, except for spastic colon. A cholecystogram showed a functioning gall bladder. The Electrocardiogram was normal.

The laboratory tests pointed in the direction of obstructive jaundice rather than hepatogenous jaundice.

At follow-up, ten weeks after leaving the hospital, the icterus index was 5, and all clinical evidences of jaundice had vanished. A diagnosis of transient obstructive jaundice was made, probably due to a calculus that was passed.

Because of the severe, distressing pruritus of which the patient complained on admission, she was given adenosine-5-mono phosphate, 20 mgs., three times daily, intramuscularly, for 2 days. Complete subsidence of the itching was evident on the morning of the second day. The patient slept well the first night without sedation. Extreme gratification accompanied relief of the itching which began to torment this patient. Following the 2nd day of the therapy, the pruritus failed to return.

TABLE I

Laboratory Tests of Patient II

Agglutination Tests were negative for Widal, Cold Agglutinin, Infectious Mononucleosis.

Stools were negative for parasites, ova and occult blood.

	10/4/50	10/6	10/9	10/16	11/3
Urea N.	10.3			11.8	
Fasting Blood Sugar	140.0			113.0	
Prothrombin Time	20 Sec.		20 Sec.		
Cholesterol	230				
Cholesterol Esters	150				
Icterus Index	34.7		24	14	18.1
VandenBergh	+Direct		Delayed	Delayed	
	+Indirect		Direct	Direct	
Alkaline Phosphatase	6 units			3.5	
Thymol Turbidity	3 units		4 units	4 units	
Cephalin Flocculation	Neg.	Neg.		Neg.	
Urine					
Bile	++	++		Trace	
Urobilinogen	+	+		+	
Erythrocyte Sedimentation Rate	7 mm (Cutler) Hr.			10 mm.	
A/G Ratio				4.6/1.35	

DISCUSSION

A5MP has been successfully used for pruritus of diverse etiologies by Rottino (4). It proved effective in pruritus associated with diabetes, Hodgkins' disease, and one case of obstructive jaundice. Based on his findings, Rottino felt that pruritus of whatever type was evidence of an adenylic acid deficiency. While we have now a fairly large series of pruritus of diverse etiologies treated with A5MP, we do not feel that this is the mechanism of action.

Green (5) has shown in a series of papers covering a large amount of careful fundamental work that adenosine triphosphate (ATP) and A5MP (6), if injected into a mouse, causes mitosis in the skin to cease. He came to the conclusion that injected ATP and also A5MP interferes with carbohydrate utilization, possibly indirectly through a hormonal mechanism and thus prevents mitosis. The anticipated hormonal mechanism was through the pituitary-adrenocortical route. This was found to be true, since following the subcutaneous injection of 1 mg. of ACTH (pituitary adrenocorticotropic hormone) skin mitosis was depressed in the mouse for several hours, similar in the way observed with ATP and A5MP.

The rate of skin mitosis is probably only a reflection of the mitosis in many other tissues, and the well-known effect of ACTH in producing lymphopenia and lymphoid tissue involution, eosinopenia, inhibition of granulation tissue formation and general inhibition of body growth may be due to suppression of mitotic activities in the various organs involved.

A recent statement by Hanger (7) would seem to be crucial for our theory: "Itching and bradycardia are common symptoms of obstructive jaundice and are usually attributed to elevation of bile salts in the blood. The level of bile salts, however, is maintained by both the rate of excretion of the kidneys and the rate of synthesis of the hepatic cells. It is common clinical experience that obstructive jaundice may cause but little itching when extensive parenchymal damage de-

presses the capacity for synthesis of bile salts by the liver." A5MP may depress the capacity for synthesis of bile salts by the liver cell just as it depresses the mitosis of skin cells. However, it does not damage the liver cell, it merely depresses temporarily some of its functions.

Precisely a similar method of action has been formulated by us for ACTH and Cortisone (8). Whether these hormones would also abolish pruritus due to common duct obstruction is not known, but this is not a crucial point since they may depress different functions of the liver cell. ACTH and Cortisone have been used successfully in the serum sickness-type of penicillin reactions. Our series of cases includes two cases of this type of reactions which responded dramatically to A5MP. In addition, two of our cases of severe status asthmaticus initially responded to ACTH, and were treated successfully with A5MP after the asthma recurred in 3 and 4 weeks respectively.

SUMMARY

1. Two patients with severe pruritus associated with calculi in the common bile duct were successfully treated with A5MP.

2. A mechanism of action was postulated for this substance.

REFERENCES

1. Steigmann, F.: Advances in the Management of Jaundice. J. A. M. A. 144:1076, Nov. 25, 1950.

2. Movitt, E.: Jaundice. Its Pathogenesis and Differential Diagnosis. New York: Oxford Medical Publications, 1947.

3. Weiss, S.: Clinical Lectures on the Gall Bladder and Bile Ducts. Chicago: Year Book Publishers, 1944.

4. Rottino, A.; Boller, R., and Pratt, G. H.: Therapeutic Action of Muscle Adenylic Acid on Ulcers and Dermatitis Associated with Varicose or Phlebitic Veins; Preliminary Report. Angiology 1:194, 1950.

Rottino, A.: Effect of Adenylic Acid Therapy Upon Pruritus due to Hodgkin's and Other Diseases. Cancer 3:272, 1950.

Rottino, A.: Relief from Pruritus following Administration of Adenylic Acid. Pro. Soc. Exper. Biol. & Med. 71:379, 1949.

Rottino, A.: The Effect of Adenosine-5-Monophosphate on Pruritus. Journal-Lancet 69:285, 1949.

5. Green, H. N.: Suggested Modes of Action of Corticotrophin in Rheumatoid Arthritis and the Allergic State. Br. M. J., 1:1165, May 20, 1950.

6. Personal communication from Professor Green.

7. Hanger, F. M.: Diagnostic Problems in Jaundice. Arch. Int. Med., 86:169, August, 1950.

8. Pelner, L., and Waldman, S.: A New Concept in Therapy: "Occupying" or "Engaging" One or More of the Liver Functions. Gastroenterology, 16:509, Oct., 1950.

The Adenosine-5-Mono phosphate used in this study was supplied as solution of "My-B-Den" by Dr. Edward K. Harvill of the Ernst Bischoff Company.

PERFORATED ESOPHAGEAL ULCER

By J. H. COFFEY, M.D. and I. DRAVIN M.D. Amarillo, Texas

In a recent article, (1) Wangensteen states that esophagitis and esophageal ulcers are manifestations of peptic ulcer which may be found to exceed gastric ulcer in frequency. Since the roentgenographic diagnosis is difficult it is often overlooked. The following report is a fairly typical case history terminated by perforation, peritonitis and death.

The patient was a 54 year old white male, first admitted in December, 1948, complaining of shortness of breath, substernal pain, nausea and vomiting for three weeks. He gave a history of "stomach trouble" for many years. The upper gastro-intestinal series showed an active duodenal ulcer with marked retention at 24 hours. The patient was placed on a progressive Sippy diet, became symptom free, gained 18 pounds, and was discharged February 7, 1949. He was readmitted April 13, 1949. He had had recurrence of burning epigastric pain and had been vomiting continuously for five days. On the morning of admission, he had vomited a large amount of clotted blood. On admission, he complained of burning pain high in the epigastrium and in the precordial region and had tenderness over the epigastrium and in both lower quadrants. He was placed on a progressive Sippy diet and was given Amphojel and tincture of belladonna. He was symptom free thereafter throughout his stay in the hospital and gained six pounds in weight. He was discharged May 10, 1949. The third and last admission was on July 26, 1949. He had done fairly well until four days prior to admission when he vomited what he thought to be about a pint of dark red blood. He continued to vomit one to two times daily and felt very weak. On the morning of admission he developed pain in the left anterior chest. There was generalized abdominal tenderness, most marked in the epigastrium. He continued to vomit gross blood and coffee-grounds material for five days after admission and complained of epigastric, substernal and right shoulder pain. For another three weeks he continued to vomit one to two times daily with occasional hematemesis and had bouts of severe precordial and substernal pain. Throughout this admission, the white blood count was elevated to between 20,000 and 30,000. An upper gastro-intestinal series showed an active duodenal ulcer with 20% residual at six hours. It was felt that gastrectomy was indicated, but the patient refused surgery. Over the next month, he improved slowly and was sent home on a two-week leave. The night following his return from leave, he suddenly developed severe vomiting

Submitted Mar. 29, 1951.

From the Medical Service, Veterans Administration Hospital, Amarillo, Texas. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

and epigastric pain, went into shock and expired a few hours later.

Autopsy revealed a generalized peritonitis secondary to a perforated esophageal ulcer. The ulcer half-encircled the lower portion of the esophagus and was connected with an abscess cavity which was walled off from the mediastinum but had perforated into the abdominal cavity. In addition, a large duodenal ulcer was found. The gall bladder was bound down to the duodenum in this area. The ulcer was found to have perforated through the wall of the duodenum and the wall of the gall bladder was acting as the base of the ulcer.

DISCUSSION:

Various causes for esophagitis and esophageal ulcer have been considered: foci of infection, inadequate blood supply, ectopic gastric mucosa and regurgitation of gastric contents. Most authors now feel that repeated vomiting is the most important factor. (1) (2) (3) Esophageal ulcer may be found at any age, but is most common in the fourth and fifth decades. Esophagitis and esophageal ulcer are frequently associated with hiatus hernia and duodenal ulcer, especially with obstructing duodenal ulcer. In a recent article, (4) 60 cases of benign esophageal stricture associated with esophagitis were described. Of these, 34 also had hiatus hernia, 20 had duodenal ulcer and 16 had active esophageal ulcer.

SYMPTOMS:

Pain—epigastric or substernal, radiating to the back and increasing during deglutition	84%
Vomiting	54%
Hematemesis	25%
Perforation	14%
Dysphagia	
Anemia	Frequent in advanced phase.
Weakness	
Weight Loss	

Hemorrhage is very frequent with esophageal ulcer, possibly due to the vascularity of the lower end of the esophagus. Esophageal ulcer in a hiatus hernia has been incriminated as the cause of some cases of obscure anemia. The incidence of perforation has been given as 14%. (2) This is probably too high, but it is certainly a not infrequent complication. The ulcer may perforate into the mediastinum or the abdomen, the latter being more common. Abdominal perforation gives the usual signs of ruptured hollow viscus. Perforation into the mediastinum gives a characteristic clinical picture. If often occurs during an attack of vomiting. There is sudden severe precordial or epigastric pain, associated with shock and dyspnea. The shock lasts for two to three hours, then the temperature rises and signs of pleural effusion develop. In 6 to 12 hours, subcutaneous emphysema may be noted in the neck. A roentgenogram of the chest may show any one or any combination of the following: air behind the heart, air in the upper mediastinum or a small pleural effusion. It is important to diagnose mediastinal perforation early since treatment by thoracotomy with drainage has proved successful in some cases. Recently, three cases were reported of mediastinal rupture of esophageal ulcers. (5) The patient's ages were 67, 70 and 73 and two of the three had chronic duodenal ulcers.

DIAGNOSIS:

An ulcer crater may be demonstrated on upper gastro-intestinal series but this is unusual. More commonly a spastic defect in the lower esophagus is found. Esophagoscopy is usually required for a definite diagnosis.

TREATMENT:

Most cases respond to the usual ulcer regime: progressive Sippy diet, aluminum hydroxide, tincture of belladonna and other medical measures. Healing may be very slow, some cases requiring three to five years. (6)

Wangensteen (1) has advocated gastrectomy for esophagitis to reduce the acidity and digestive capacity of the contents of the residual gastric pouch and quicken the gastric emptying time. He has had excellent results in intractable cases.

CONCLUSION:

The possibilty of esophagitis or esophageal ulcer should be considered in patients with burning substernal or epigastric pain occuring during or shortly after meals, especially if upper gastro-intestinal series is negative or a hiatus hernia or obstructing duodenal ulcer is found.

REFERENCES

1. Gastric Resection for Esophagitis—Wangensteen & Leven S. G. & O. 88:560: 1949.
2. Peptic Ulcer of the Esophagus—Friendenwald, Feldman, Zinn—Am. J. Med. Sci. 177:1: 1929.
3. Esophagitis—Butt & Vinson—Arch of Otolaryngology—23: 391: 1936.
4. Benign Stricture of the Esophagus—Benediet & Sweet — Gastro-Enterology 11:618: 1948.
5. Perforation of the Esophagus—Hertzog & Leighton — Minn. Med. 29:442: 1946.
6. Peptic Ulcer of the Esophagus—Chevalier Jackson—J. A. M. A. 92:369: 1929.

ABSTRACTS ON NUTRITION

CASTLE, W. B.: *Present status of the etiology of pernicious anemia.* Ann. Int. Med., 34, 5, May, 1951, 1093-1106.

Castle now regards pernicious anemia as a conditioned deficiency of vitamin B_{12}, the latter being identical with the extrinsic factor, and incapable of absorption in useful amounts in the absence of the intrinsic factor in the gastric juice. Intrinsic factor is secreted by those portions of the human stomach that are found to be degenerated in the disease, pernicious anemia. The use of even large doses of folic acid in pernicious anemia presents no hazard to the nervous system provided the amounts of vitamin B_{12} usually employed in the treatment of

pernicious anemia are injected at monthly intervals. Both vitamin B_{12} and folic acid are required for normal hematopoiesis and perhaps also for the functional integrity of the digestive tract and nervous system in man. The red cells in persons with pernicious anemia have a shortened life span, 72 days, as compared with 120 days in the normal subject. Defective diets and intestinal dysfunction or disease, especially when gastric secretion is not significantly disturbed, may result in nutritional macrocytic anemia in which the predominant deficiency is not of vitamin B_{12} but of folic acid. Ascorbic acid is apparently required for normal hematopoiesis. The relationship of vitamin B_{12}, folic acid and ascorbic acid to the nucleoprotein metabolism is not disclosed.

HUTTON, J. H.: *Obesity—diagnosis and treatment.* Illinois Med. J., 99, 5 May 1951, 237-242.

While Hutton admits our dearth of knowledge with respect to the true causes of obesity, he produces an unusually interesting discussion of possible factors. Likewise in treatment, his use of Antuitrin in certain cases seems to be of benefit. He regards obesity as one of our major problems today.

MENEGHELLO, J. AND NIEMEYER: *Liver steatosis in undernourished Chilean children. III. Evaluation of choline treatment with repeated liver biopsies.* Am. J. Dis. Child., Dec. 1950, 905-910.

All children with liver steatosis associated with plurideficiency dystrophy were given high protein, low fat diets. Approximately half of them received daily 5 gm. of choline hydrochloride over a period of not less than 10 days, and this group showed definite acceleration in the removal of fat from the liver. The other group which received no choline displayed a much slower fat removal. Choline was thus shown to exert a definite lipotropic action in this form of liver disease.

WEINSTEIN, A.: *Coronary thrombosis and diabetes mellitus: The influence of coronary thrombosis on the metabolism of the diabetic patient.* Am. Pract. & Dig. Treat, 1, 12, Dec., 1950.

Weinstein describes two cases of diabetes in whom the onset of coronary thrombosis was associated with an unfavorable disturbance in the carbohydrate metabolism. This may occur before the electrocardiographic picture has become diagnostic. The appearance of acidosis or an increase in the severity of the diabetes may herald the beginning of coronary thrombosis.

GREEN, M. B. AND BECKMAN, M.: *Supplement protein in weight reduction.* Am. Pract. & Dig. Treat., 1, 12, Dec., 1950.

To prevent negative nitrogen balances during weight reduction, an intact casein derivative mixed with "a carbohydrate derived from sugar" (Protinal) was used as a supplement to the diet. Good results seem to have been obtained. dl-desoxyephedrine was given to curb the appetite.

NEWCOMB, A. L.: *Diabetes mellitus in infants and children.* Illinois Med. J., 99, 4, Apr., 1951, 204-206.

The pregnant diabetic requires good control of the diabetes and hormonal substitutional therapy with delivery at the 38th week, by means of section under spinal anesthesia, in order to avoid toxemia of pregnancy. The newborn infant of the diabetic woman is large, edematous and often jaundiced. Respiratory embarrassment, instability of the blood sugar, splanchnomegaly and erythroblastosis are frequently present. Delay in tying the cord serves to donate placental blood to the infant. Gastric aspiration and the use of oxygen are beneficial. Glucose in the first few hours is advisable because of frequent pancreatic hypertrophy. Many believe a "free diet" with adjustment of insulin to glycosuria is advantageous in infants showing diabetes.

ALLEN, G., AND CRITCHLEY, C. F.: *Macrocytic anemia.* Brit. Med. J., Mar. 31, 1951. 677-679.

The authors describe the case of a 35 year old man, with weight loss, gastrointestinal symptoms, and a macrocytic anemia. The condition developed after surgical procedures which led to stasis of the small bowel and was cured solely by surgical removal of the lesion, without the use of any form of medicine. The case obviously is similar to those previously described by Seyderhelm. The anemia is apparently due to some interference with the absorption (or to some destruction of) blood maturation factors. Short-circuit operations below the stomach are unsound except as temporary measures.

METZ, H. A. AND ODENDAAL W. A.: *The role of the B-vitamins, lysine, and tryptophane with respect to growth, the inactivation of the estrogens in the liver and sex physiology.* South African J. Med. Sci., 15, 4, Dec., 1950, 83-100.

In an experimental study on rats, the relationship was investigated between certain aspects in nutrition, the function of the liver with respect to the inactivation of sex hormones, sex physiology and growth. Maize was used as the basic foodstuff, supplemented with amino acids (lysine and tryptophane) and B-vitamins (natural and synthetic) and compared with fixed standard mixtures. The extent of growth was obtained by weighing the animals weekly. Daily vaginal smears provided an index of the amount of estrogens inactivated in the liver, before and after intrasplenic implantation of estrone pellets. It was concluded:—Maize as the sole food source causes a condition of starvation. The nutritional value of maize can be improved by the addition of lysine and tryptophane but is decreased by the addition of synthetic B-vitamins alone. Although normal growth may be obtained by a synthetic B-vitamin mixture, the latter does not maintain normal sex functions. B-vitamins are essential for the liver function with regard to estrogenic inactivation, possibly more so than the amino acids mentioned. A certain balance between the different members of the vitamin B-complex is essential for the inactivation of optimal quantities of estrogens. Stimulation of growth increases the utilization of vitamins which are essential for estrogenic inactivation. Borderline nutritional deficiencies may cause hyperestrogenism. Yeast as a natural source of B-vitamins is of more value than synthetic mixtures. A balance must exist in the diet between proteins (amino acids) as the "building stones" of the body and vitamins which stimulate growth.

KLENNER, F. R.: *Massive doses of vitamin C and the virus diseases.* J. Southern Med. & Surg., CIII, 4, 101-107, Apr., 1951.

The author reports pre-measles arrested by injection of vitamin C in two cases, a case of encephalitis apparently arrested by vitamin C. Pulmonary virus infection in two cases likewise responded. He also uses it in treating anterior poliomyelitis.

LISTER, J., NASH, J. AND LEDINGHAM, U.: *Constitution and insulin sensitivity in diabetes mellitus.* Brit. Med. J., Feb. 24, 1951, 376-379.

The authors have designated a group of diabetics of characteristic physique who are almost uniformly insensitive in their response to insulin. They describe the physical characteristics of this group in detail. Other diabetics, not falling in this group, are of an "unremarkable" constitution. (One fifth of all patients examined were intermediate in type and could not be classified). The "unremarkable" group showed a mean insulin sensitivity of 0.48 while the remarkable group had a sensitivity of 0.78. They could not define precisely the effect of weight on insulin sensitivity, but probably in most cases the actual sensitivity of a patient is a fundamental constitutional characteristic.

GIRDWOOD, R. H. AND CARMICHAEL, K. M.: *The content of hemopoietic factors in liver extracts: relationship to clinical response.* Brit. Med. J., Dec. 16, 1950.

The vitamin B_{12} content of 15 batches of British liver extracts prepared for commercial use between 1945-50 and tested microbiologically by a tube method using *L. leichmanii* as the test organism was low, varying from 0.25 micrograms to 7.6 micrograms per c.c. The pteroylglutamic acid content was negligible. The actual rise of red cells in 20 pernicious anemia patients treated with these liver extracts was compared with the calculated response according to the vitamin B_{12} content. The results gave no evidence to suggest that the hemopoietic responses could not be attributed to the vitamin B_{12} content of the liver extracts. There should be a standardization of methods employed in the microbiological assay for vitamins B_{12} content.

DODDS, E. C.: *Protein structure and clinical problems.* Brit. Med. J. Dec. 2, 1950.

In an inspiring address, Dodds elaborates on the basic protein structure of enzymes, antibodies and hormones, as well as viruses and emphasizes that the millions of complex protein molecules in the body are built to exact formulas by some, as yet, mysterious controlling mechanism. The whole protein of the body is replaced every 160 days. When the controlling mechanism finally is understood, we shall find the answer to many problems, possibly even the mechanisms of senescence and of cancer.

SINCLAIR, R. J. G. AND DUTHIE, J. J. R.: *Intravenous iron in treatment of hypochromic anemia associated with rheumatoid arthritis.* Brit. Med. J., Dec. 2, 1950.

A satisfactory rise in hemoglobin levels was obtained by intravenous injection of iron in about 70 per cent of cases of hypochromic anemia associated with rheumatoid arthritis, all cases having previously been shown to be resistant to oral iron. The preparation used was "ferrivenin". Cases responding showed a rapid fall in the erythocyte sedimentation rate. In rheumatoid arthritis there seems to be an increased demand of the tissues for iron. No toxic reactions are reported.

DAVIS, N.: *Hepatitis: treatment with brewer's yeast.* Med. J. Australia, Nov. 25, 1950, 790-92.

In addition to complete rest, Davis uses a high caloric diet (140 gm. protein, 400 gm. carbohydrate, 70 gm. fat). The patients also received daily 12 gm. of dehydrated brewer's yeast powder. The series of 126 patients included none with advanced cirrhosis of the liver. Cure was obtained in 20 cases, 40 were improved, 52 relieved, 4 unrelieved and 1 died.

EDITORIAL

NORMAN LOOKS AT ULCERATIVE COLITIS

The complete title of this new book* by Norman is,—"Postulating a new concept of chronic ulcerative colitis—is it a hemorrhagic disease caused by multiple nutritional imbalances?" The author had four or five distinct aims in writing this unusual monograph: to enunciate a new etiological hypothesis; to review the pathology; to emphasize the importance of natural (unprocessed) foods in all health schemes; to describe a series of cases, most of whom were apparently cured by his scheme of concordant meal planning; and, finally, to familiarize the reader with a type of concordant meal planning which thus far has never become popular with the medical profession, the academic nutritionists, or food industry technologists. Moreover, he emphasizes the necessity for *teaching the patient a new perspective* regarding the confused nutritional environment in which he lives and functions and how, with this precise scheme of meal planning, he can dispense with processed foods and at the same time improve his dietary. Since each of these aims is fairly iconoclastic, the book is challenging rather than convincing.

Norman regards ulcerative colitis as a multiple deficiency disease, the outstanding dietary deficiencies being vitamin C, the P flavonols and vitamin K. Since these nutrients are obtained from fresh vegetables and fruits, and since the latter are usually excluded from ulcerative colitis diets because of their roughage content, the theory may not be without plausibility. These alleged deficiencies profoundly disturb the blood clotting mechanism and the integrity of the capillary tissues which govern the factors of normal permeability and fragility. The hemorrhagic aspect of the disease is not only emphasized but is found to be the main and underlying aspect, placing the malady among the hemorrhagic diseases. Such a pathological interpretation is rather difficult to dispose of in any summary manner. Many physicians will feel that Norman has scarcely done justice to the thrombotic aspect of the disease. In some cases, at least, thrombosis has been regarded as the immediate cause of the intestinal ulcers and it is the consensus that bleeding occurs chiefly from the ulcerated areas. The reason for this divergence of opinion is because Norman feels that the constant oozing or leakage of blood through what he calls "the hemotumescent areas of mucous membrane" is more constant and greater than from the ulcerated areas. Moreover, he apparently considers ulcers as focal points of necrotic tissue erosion in a hemotumescent mucous membrane in which there is a profound disturbance of the capillary bed, the function of the intracellular ground substance (hyaluronic acid-hyaluronidase balance), the lysis of protective mucous by excessive lysozyme, plus the cumulative effect of the nutritional deficiency factors upon capillary fragility and permeability.

Norman does justice to other etiological theories, and while he sees sense in infectious, psychoneurotic and allergic influences, he regards them as accessory and contributory, but not fundamental. He makes a point which is challenging—which comes first—improper nutrition, infections, psychoneuroses, or allergies? According to the observations of many nutritionists, it would seem that improper nutrition prepares the soil for the genesis of infections, psychoneuroses and allergies. Of course, this represents the perspective of the newer school of nutritional thought.

The portion of the book which describes some 55 cases of ulcerative colitis is the most challenging because in 53 of the cases, Norman claims complete cure (judged by very critical standards) and states that cure was due solely to the use of natural foods, fed by a special meal-planning regime. Granting the validity of such hitherto unparalleled therapeutic results, it of course does not automatically follow that the results prove the etiological theory to be correct. The outstanding alleged fact is that apparently cures were achieved basically through a dietary form of treatment.

Norman regards his scheme of meal planning to be as essential as the use of natural foods. The philosophy of his scheme of concordant meal planning is predicated upon the controversial question as to whether or not the combination of concentrated proteins,

*"A New Concept of Ulceration Colitis." N. Philip Norman, M. D., 168 pages. Lee Foundation for Nutritional Research, Milwaukee, Wisc.

concentrated carbohydrates and concentrated fats, can be efficiently digested by antagonistic digestive processes in the same vat. He feels that Pavlov has supplied the answer and presents graphs and excerpts from Pavlov's book to support his contentions.

Pavlov's digestive experiments led him to believe that starches, fats and proteins, ingested singly, initiated a secretory stimulus on the part of the gastric and duodenal glands which were specific and selective in constitution for each. Every medical student studies Pavlov's work as part of his course in physiologic chemistry. Norman takes the position that the importance of this portion of Pavlov's work has been lost to medicine because it has never been thoroughly investigated and only sporadically used by independent investigators in the field of applied nutritional therapy.

Few physicians will deny that food-processing has, in many ways, degraded the nutritional value of certain food items and it is becoming clearer, year by year, that any serious divergence from a strictly normal food base carries potential trouble for a populace. The progress of food analysis at the Massachusetts Institute of Technology has indicated that the crude foods consumed by certain primitive tribes, now living, provides much higher amounts of most essential nutrients than are currently being obtained in the average American diet. Several nutritional surveys as well as the medical records of disqualified draftees and inductees in World Wars I and II, respectively, substantiate the contentions of many nutritionists that despite our ample food supply, a large percentage of the population is inadequately nourished. Studies and observations by competent authorities place the blame for this on many factors—chiefly depleted soils, lack of seed culture, induced changes in agricultural practices and in animal and in poultry husbandries, improper harvesting and storage practices, food losses through transportation and distribution, and finally what cooks and housewives do to it in the kitchen. While Norman's criticisms of what is wrong with the American diet are undoubtedly largely well-founded, his exhortative style, in these passages, is in such contrast to his scientific prose, that it robs the book of a literary unity it might otherwise have possessed.

Ulcerative colitis, as we are all aware, is a peculiar disease, cases of which at times seem to respond favorably to the most bizarre forms of treatment. The reviewer knows one case which was rather quickly (and permanently) *cured* by a dietary of raw carrot juice—a treatment which the patient invented for himself.

Norman's book is valuable as an unusual record of striking results in ulcerative colitis through the use of natural foods. This point transcends his etiological hypothesis and perhaps his peculiar meal-planning, and constitutes a fascinating finding which, if ever confirmed, would in time exert a revolutionary influence on the science of applied nutrition. But until his work has been duplicated by others, it must remain strictly *sub judice*.

BOOK REVIEWS

A CLASSIFIED BIBLIOGRAPHY OF GERONTOLOGY AND GERIATRICS, by Nathan W. Shock, Stanford University Press, Stanford, California. $15.00.

TRENDS IN GERONTOLOGY, by Nathan W. Shock, Stanford University Press, Stanford, California. $2.50.

Particularly significant to the medical profession and of great interest to the informed public is the announcement of the publication by Stanford University Press of Dr. Nathan W. Shock's "Classified Bibliography of Gerontology and Geriatrics," and its companion, "Trends in Gerontology."

Distinguishing between the two terms, "gerontology" and "geriatrics," Doctor Shock points out that gerontology is the scientific study of the phenomena of the aging. All living matter changes with time in both structure and function, and the changes which follow a general trend constitute aging. Aging begins with conception and ends with death. Growth, development, and maturation are thus a part of the aging process just as much as are atrophy and degeneration.

Geriatrics is defined as that branch of medical science concerned with the medical and pathological problems of older individuals. It includes methods for maintaining health and vitality as well as the treatment of disease states in older people, and is thus a part of the broader field of gerontology.

Because the maximum human age-potential is becoming increasingly higher, Dr. Shock's monumental contribution is a timely attempt to clarify what was previously a disassembled, miscellaneous array of subject material.

The "Classified Bibliography" includes over 18,000 references in fourteen languages. The references have been classified in small sub-groups, so that each contains less than 150 items. The major divisions of the "Classified Bibliography" are: Gerontology, General Orientation; Biology of the Aging; Organ Systems; Geriatrics; Psychological Process; Social and Economic Aspects; and Miscellaneous.

"Trends in Gerontology" summarizes the efforts to solve the problems of the aging in regard to employment, health maintenance, living arrangements, education, community programs, care, and rehabilitation.

To meet the demands of these problems more effectively, Doctor Shock recommends that an "Institute of Gerontology" be founded, and outlines in detail the organization and function of such an institution.

"Thus broadly conceived, the functions of an Institute of Gerontology should be research, teaching, and service to the aged," the authority explains. "Ultimately, such an Institute should co-ordinate and utilize the full capacities and potentialities of both a local and university community."

Doctor Shock is careful to explain that his work is not a magic cure-all for the problems confronting the aged and those responsible for their care; it is a compilation of all existing knowledge that could be uncovered by research workers over a period of years.

The material in "Trends in Gerontology" was assembled by personal visits to research laboratories, old people's homes, housing projects for elderly people, recreation clubs, institutes, community projects for old people, and organizations interested in the welfare of the elderly. In addition, research reports published since 1940 were analyzed.

Complete and carefully scaled graphs and charts accompany the text to show more clearly how geography, housing facilities, employment conditions, and health programs affect life-expectancy at decennial ages, assuming elimination of specific causes of death.

The underlying overtones of "Trends in Gerontology" ultimately combine to further the hope that, potentially, society's aged members will face a future assured of more independent and useful participation within the society in which they live.

With the publication of the "Classified Bibliography," under a grant from the Forest Park Foundation of Peoria, Illi-

nois, physicians, welfare workers, and interested persons have, for the first time, an indexed, catalogued reference to aid them in their never-ending search for the answers to the question: How can I live a more comfortable and more useful old-age?

THE BASES OF HUMAN BEHAVIOR. Leon J. Saul. 150 pages. J. B. Lippincott Company, Philadelphia. 1951. $4.00.

The book is designed to provide, in simple form, the fundamental knowledge upon which modern dynamic psychiatry rests. Its purpose is to give the reader an appreciation of the reality of the emotional forces within the mind, their sources in the biology of the organism and something of their relationship to its physiologic functioning. It aims also to convey the present-day concept of the structure and development of the mind. Thereby it leads up to the study of the major emotional forces in the mind and their interplay.

The first part of the book deals with the place, the scope and the goals of dynamic psychiatry. In the second part, it is shown how emotional forces can affect the physiology and produce symptoms, and tissue damage. The effect of emotional forces on perception, thinking, feeling, and behavior is discussed in another chapter. Under the heading of "Elements of psychodynamics" the id, the superego and the ego are discussed. A special chapter is devoted to the development of the mind. In an appendix, the nature of neurotic reactions is described.

The book is very well written, and can be only highly recommended to all interested in this field.—Franz J. Lust.

CLINIC AND THERAPY OF MASSIVE GASTROINTESTINAL HEMORRHAGE (Klink and Therapie der massiven Magendarmblutung). Nicola Markoff. 136 pages with 31, partially colored illustrations, 16 tables. Verlag Hans Huber, Bern, Switzerland. Grune & Stratton, New York. Sw. Fr. 14.20.

This is the second in a series of monographs covering internal medicine and its borderline fields. It discusses the question of the increase of peptic ulcers during the past years, especially the large ulcers with anacidity and hypoacidity. The author is of the opinion that every haemorrhage should be hospitalized. In the beginning the treatment of shock is of prime importance. Blood transfusions with large amounts of vitamin C and K should be given. As soon as shock is over, the interval to the next bleeding should be used for further diagnostic investigation. The roentgenological examination is of greatest value. A negative bromsulfalein test would exclude bleeding from varices. Conservative treatment in patients under 45 years gives good results. In patients over 45 years, surgical intervention is nearly always necessary. Nineteen case reports illustrate the findings. There are excellent roentgenograms and gastroscopic pictures in the book. The roentgenograms of varices in the fundus of the stomach and in the cardia seem to be the first published of such cases.

This very interesting book can be only recommended to all gastroenterologists and specialists in internal medicine and surgery. The question of gastroduodenal haemorrhage is not solved and Markoff's book is an important contribution in this field.

Print and illustrations are of the highest standard.—Franz J. Lust.

THE HUMAN COLON. William J. Grace, M.D., Stewart Wolf, MD. and Harold G. Wolff, M.D., 239 pages, Paul B. Hoeber, Inc., New York, 1951, $7.50.

The living colon, exposed through fistulous openings, has been studied in four highly cooperative patients. Direct observations were made on the effects of pharmacologic and physical agents as well as of emotions on the colon. Evidence is provided by these unusual studies which links emotion to functional disorders as well as to structural lesions with actual organic tissue changes. Most readers are already familiar with this work of the authors and will be delighted with the book not least because of the beautiful color illustrations. The treatise really furnishes new and striking evidence for the validity of the unitary concepts of psychosomatic medicine. It is most highly recommended.

DE RE MEDICA. Eli Lilly Company, Indianapolis, 1951.

643 pages of valuable medical information, in a book most handsomely bound, constitute a pleasant presentation from a well-known pharmaceutical firm. It may be characterized as a condensation of therapeutic suggestions in common diseases. The action and uses of drugs, laboratory tests, poisons and antidotes form the bulk of the work, while there is also a section of color plates and a further section of useful tables of various sorts. At the very end is a selected list of Lilly Products. The book is an example of the helpfulness of a large pharmaceutical company, as well as an example of the beautiful book-making employed. The volume can be safely lifted off the desk by any one page.

GENERAL ABSTRACTS

REYNOLDS, J. T. AND PEARSE, H. E., *Radical Pancreatico-Duodenectomy.* (Surgery 25, 6, 815, June, 1949).

The question has been widely discussed whether after radical Pancreatico-Duodenectomy the opening of the pancreatic duct, transplanted into the jejunum remains patent. Authors contribute the autopsy findings of 2 cases with a radical operation 6 months and 22 months previously. In one case a Blakemore Vitallium tube was used for the anastomosis, in the second the suture was done over a ureter catheter. In both cases the opening of the pancreatic duct was found patent and the pancreatic tissue showed normal appearance. Authors advocate the use of an internal splint which necessitates relatively little handling and damage to the delicate wall of the pancreatic duct.

GREENFIELD, J. AND SANDERS, J. H., *Total Pancreatectomy with reports of postoperative physiologic studies.* (Surgery 25, 6, 824, June, 1949)

The following physiologic studies were carried out in a 58-year-old colored male after total Pancreatectomy for Carcinoma.

During the immediate postoperative period a 6-hour emergency acidosis regime was established. One unit of regular Insulin was given to every 2 Gm. of Glucose, administered intravenously. Blood sugars were determined twice daily. When the latter rose above normal values more Insulin was administered. The greatest fluctuations of the Blood-Glucose levels occurred during the first five days, varying from as much as 400 mg. per cent in the evening to 95 mg. per cent in the morning. These fluctuations were independent from the parenteral administration of Glucose and fluids, for these were spaced evenly throughout the 24 hours period and the blood-glucose samples were taken before the glucose was administered. 80 units of regular Insulin were given during the second post-operative day, and the amount decreased to 40 units in divided doses every 6 hours. A considerable amount of glucose was present in the urine after the 23 post-operative day. However Protamin Zinc Insulin (40 units) plus 10 units regular has proved too much. Eventually 40 units Protamin Zinc-Insulin was established as sufficient dosis.

Liver-tests: *Serum-Bilirubin* remained for 7 days at the preoperative level then fell gradually to normal in 65 days. *Alkaline-Phosphatase* was 14.6 King-Armstrong units preoperatively and dropped slowly to normal in 90 days. *Blood-Cholesterol* values varied in wide range to be normal on the 90 day. *Cephalin-Flocculation* was plus 4 preoperatively and became negative after 34 days. Thymol test was normal. Serum-Amylase was 54 mg. per cent the day following surgery and varied between 18 and 75 mg. in the ensuing 6 months. Total Protein and Albumin-Globulin ratio remained normal. Ketosis developed only during an intercurrent infection (cellulitis of the jaw).

Diet: Caloric intake was gradually increased to 2803 Calories (404 gm. C. H., 182 gm. Proteins, 51 gm. fat.) Pat. regained

appetite not until the 46 post operative day. 3 gm. of Methionine was given from the 15 post-Op. day. Pat. maintained his pre-op. weight of 160 pounds. Pancreatin-tablets (16 gm. daily) have proved valuable. *Stool*: was diarrheic the first 12 post-Op. days (6-8 liquid evacuations). Analysis revealed that 128 gm. dry fecal solids, compared to 40 gm. normal. 30 per cent was fat (27.9 per cent fatty acids and 2.8 per cent neutral fats), Protein made up 27.9 per cent of the total dry fecal solids.

Discussion of interesting findings: With 40 units of Insulin Diabetes was controlled. Ketosis appeared only during an intercurrent infection. No marked Liver-dysfunction was found. Fat-splitting into fat acids was found amazingly high in spite of absence of pancreatic enzymes.

GLENN, FRANK. *Present status of the surgical treatment of peptic ulcer.* (J. A. M. A. 145, 11, 785. March 17, 1951).

At the present time three procedures are commonly employed in the surgical treatment of peptic ulcer. These are gastric resection, gastroenterostomy and vagotomy either alone or in combination with the other two. A series of 414 patients is reported who were treated by gastric resection in 309 instances, gastroenterostomy in 35 and vagotomy, either alone or in combination, in 84, a total of 428 operations. The mortality rate associated with gastric resection was 1.9%. The follow-up results of an earlier group of gastric resection patients combined with the group reported indicate 87% satisfactory results 5 years after operation. Gastroenterostomy, once the procedure of choice, has been replaced by gastric resection. In the 414 patients reported it was used only as a compromise procedure when gastric resection was contraindicated. Vagotomy has been used alone in 60 instances and combined with gastroenterostomy, gastric resection or cardioplasty in 24 cases, with an operative mortality of 1.1%. Twenty-one of the 82 vagotomy patients, or 25.6%, are considered to have poor or unsatisfactory results on follow-up studies made within four years of operation. Studies made on a series of 113 patients requiring secondary operations for peptic ulcer indicate that in less than half recurring symptoms developed within 5 years of the primary operation.

At present, it is Glenn's opinion that a gastric resection which removes the ulcer and from 65 to 75% of the stomach is the procedure of choice for the surgical treatment of peptic ulcer. In the normal run of such patients there are some, perhaps under 10%, for whom gastric resection is contraindicated. For these, gastroenterostomy is indicated, as a compromise procedure, but with the plan in mind to do a gastric resection later when and if possible. It is recognized that marginal and jejunal ulcers may occur following gastric resection, but they are believed to recur in well under 10% of the group. For these, vagotomy is recommended. By and large, the immediate results from vagotomy are excellent, but recurrence may still take place even after its employment as a secondary procedure. In that event, total gastric resection could be considered.—Franz J. Lust.

SHARPE, MYER AND GOLDEN, ROSS: *End-to-end anastomosis of the colon following resection.* (Am. J. Roent. Rad. Ther. 64, 5, 769, Nov., 1950).

Forty-two cases of resection of the colon with end-to-end anastomosis were studied by barium enema from a few weeks to more than 7 years after operation. 36 of these operations were done for carcinoma of the colon. 39 showed some abnormality at the site of the anastomosis at the first examination following operation. The abnormality was a constriction, which was less than 1 cm in length in 27 and more than 1 cm in 12; it was bilateral in 35 and unilateral in 4. A structural change in the wall resulting from the anastomosis is probably the cause of most of the short constrictions. Spasm adjacent to the anastomosis seems to play a part in the longer bilateral constrictions and in this series the spastic element diminished or disappeared with the elapse of time except in one case with abdominal carcinomatosis. One short bilateral constriction was no longer present 25 months after the first examination and 35 months after the operation. Unilateral narrowing at the site of anastomosis was associated with local recurrence of carcinoma in 3 and with a local adhesion in one of 4 cases.—Franz J. Lust.

DR. M. RATSCHOW AND DR. H. BODECKER: *The Significance of Star Angioma in the Diagnosis of Liver Diseases.* (Neue Medizinische Welt 1, 44. 1939, Nov., 1950).

Star angioma was found to be a sign of cirrhosis of the liver by Eppinger. Twenty patients with cirrhosis of the liver had, without exception, star angioma. This sign was always present before a fully developed picture of cirrhosis of the liver was found. In patients with liver damage, it was possible in 20% to demonstrate star angioma of otherwise non-visible cases, by venous stasis after novocaine blocking of the ganglion stellatum. The authors think that star angioma is a partial symptom of a general angiopathic reaction which results in an increased tendency to vascular spasm. It is possible that centrally caused angiopathy is the cause of transforming a liver damage into a cirrhosis of the liver. The significance of the symptom is emphasized.—Franz J. Lust.

DOWNIE, E.: *Etiology of diabetes mellitus.* (Med. J. Australia, Jan. 20, 1951, 110-113).

Downie thinks that diabetes mellitus should be regarded as a symptom complex resulting from any one of a number of causes rather than as a disease *sui generis*. The one essential feature of the disease is abnormal hyperglycemia. In at least some instances this may arise from an increased utilization or destruction or inhibition of insulin rather than from a primary decrease in its production.

KING, W. E.: *Pathological aspects of diabetes.* (Med. J. Australia, Jan. 20, 1951, 113-114).

King stresses 3 main pathological features of diabetes,—the presence of glycogen in the liver cell nuclei, and certain lesions in the glomeruli and papillae of the kidney. The frequency of papillary necrosis is now coming to be generally recognized. While these three changes may be found in non-diabetics, their presence in a definite, recognizable form may be taken as pathological evidence that the patient suffered from diabetes mellitus.

HUNT, B.: *Why diet the diabetic?* (Med. J. Australia, Jan. 20, 1951, 114-117).

Hunt does not believe that rigid dieting is necessary in diabetes. He regards a diabetic as one who cannot in his own body produce enough functioning insulin for his needs. He does not feel that the diabetic has anything else fundamentally wrong with him. The giving of sufficient insulin to make up the deficiency makes him a normal person. Consequently he should use a normal diet.

MCCORMICK, W. J.: *Vitamin C in the prophylaxis and therapy of infectious diseases.* (Arch. Pediatrics, 68, 1, Jan., 1951, 1-9).

The author attributes the uniform decline in infectious diseases to some undetected overall factor and suspects that the wider use of vitamin C in citrus fruits may be the reason. He reviews the effects of ascorbic acid on many infectious diseases in support of his hypothesis.

DUNNE, E. F., JENSEN, E. H. AND HUGHES, C. R.: *Preliminary study of a new cholecystographic medium.* (Cleveland Clin. Quart., 18, 2, April, 1951, 98-101).

The authors report on comparative trials of Priodax and a new compound known as Telepaque. In a series of 232 patients, Priodax was used in 116 and Telepaque in 116, and such side-effects as nausea, vomiting, diarrhea and dysuria, as well as the clarity of gall bladder visualization were tabulated. There was a significant reduction in the number of side effects with Telepaque in comparison with Priodax. Furthermore, adequate visualization was obtained with Telepaque. Telepaque is a cream-colored solid, containing 66.68 per cent iodine by weight, in organic combination (compared with 51.38 per cent in Priodax).

WELLS, C. AND WELLBOURN, R.: *Post-gastrectomy syndromes. A study in applied physiology.* (Brit. Med. Jour., Mar. 17, 1951, 546-554).

The authors divide the post-gastrectomy snydromes into (a) Early syndromes in which increased tension in the jejunum is produced, (b) Late syndromes due to hypoglycemia, (c) De-

ficiency syndromes,—loss of weight, anemias of various types and vitamin B deficiencies.

CALOV, W. L.: *Indications for splenectomy.* (Med. J. Australia, II, 18, Oct. 28, 1950).

Hypersplenism is a condition of overactivity on the part of the spleen and it may be primary or secondary to such diseases as leukemia, Hodgkin's disease, rheumatoid arthritis, syphilis, miliary tuberculosis and malaria. It may be merely an incidental feature or it may be the main feature of the illness. In the latter case, splenectomy is advisable. In the former case, it is advisable only when the operation will improve the patient's chances of recovery. Splenectomy is correct treatment in familial acholuric jaundice. In acquired hemolytic anemia, the operation is not so likely to be of value, but at times it is curative.

SEGAR, L.F.: *Jaundice during pregnancy.* (Harper Hosp. Bull., 8, 6, Nov.-Dec., 1950).

The case is reported of increasing jaundice in a 28-year-old primipara, first noted at 5 months. It was impossible to designate the cause of the jaundice. Infectious hepatitis and homologous serum jaundice were ruled out, and so was calculus and cancer, but there was a possibility of acute yellow atrophy. Pregnancy was terminated by Caesarean section, obtaining not only a viable child but also the diagnosis. Liver biopsy specimens showed biliary cirrhosis. Clinically the patient has been improving since operation. Apparently the case represents an unrelated coincidence of pregnancy in a woman who was developing biliary cirrhosis.

FULTON, H.: *Leiomyoma of the esophagus.* (Harper Hosp. Bull., 8, 6, Nov.-Dec., 1950).

Benign tumors of the esophagus are so rare that from 1717 to 1932 only 63 case reports could be found in the literature. The author describes a case in a 36-year-old white male patient who was cured by operation. The tumor was intramural. Diagnosis usually depends on x-ray studies of the esophagus. Some chest pain and dysphagia was present.

SEIFE, M., KESSLER, B. J., HOFFMAN, J. AND LISA, J. R.: *A clinical, functional, and needle biopsy study of the liver in pulmonary tuberculosis.* (Am. Rev. Tuberculosis, 63, 2, 202-208, Feb., 1951).

Seventy patients with pulmonary tuberculosis were investigated by liver function tests, and biopsy of the liver. The commonest lesion found was nonspecific focal necrosis, always intralobular and frequently periphlebitic, but tubercle formation was infrequent. Fatty change was moderately frequent and was more related to undernutrition than to tuberculosis per se. Cirrhosis was more closely related to alcoholism and nutrition than to tuberculosis. A low total serum cholesterol was more frequent with far advanced lesions and more closely paralleled the clinical course than any other functional test.

PERSKY, M.: *Sodium caprylate treatment for thrush.* (Arch. Pediatrics, 68, 1, 33-34, Jan., 1951).

A 10 per cent aqueous solution of sodium caprylate cleared up 12 cases of thrush in an average of 4 days without complications or recurrences. Keeny in 1939 had found this substance to be an effective fungicide. Persky rubs the solution into the tissues of the tongue and cheeks four times daily. (He obtained the sodium caprylate from Dr. J. A. Morrell of the R. J. Strasenburgh Co., Rochester, N. Y.).

FORCHHEIMER, F.: *Anorexia nervosa in children* (Arch. Ped., 68, 1, 35-45, Jan., 1951).

This reprint of a paper read in 1907 developed the hysterical aspects of infantile anorexia nervosa and stressed isolation in its treatment. Gavage seldom was required.

LAMBIN, P. AND LEDERER, J.: *Relationship of blood dyscrasias to the diseases of the esophagus, stomach and duodenum: Medical aspects of the problem.* Acta Gastro-Enterologica Belgica (Supplement, May, 1951) 316-357.

The authors discuss the relationship between gastric acidity and iron absorption, the intrinsic factor of Castle, the Plummer-Vinson syndrome, chlorosis, pernicious anemia, pregnancy anemia, dibothriocephalus anemia, hemolytic anemias, polycythemia and several other syndromes.

DESNEUX, J. J.; *Gastroscopy in blood dyscrasias.* Acta Gastro-Enterologica Belgica (Supplement, May, 1951), 419-443.

Desneux says that no lesion of the gastric mucosa can be found gastroscopically which is characteristic of a disease of the blood. The exception is lymphatic leukemia, where the lymphoid infiltration may be diagnostic.

BROMBART, M.: *Some aspects of radiology of the esophagus, stomach and duodenum in relation to blood dyscrasias.* Acta Gastro-Enterologica Belgica (Supplement, May, 1951), 445-461.

Diaphragmatic hernia is important to rule out in cases of severe anemia. The frequency of the finding is directly proportional to the frequency and persistency with which the lesion is looked for. In all anemias of undetermined cause the clinician should consider the possibility of a benign tumor of the upper digestive tract, and these should be routinely looked for.

RAPPAPORT, E. M., ROSSIEN, A. X. AND ROSENBLUM, L. A.: *Arthritis due to intestinal amebiasis.* (Ann. Int. Med., 34, 5, May, 1951, 1224-1230).

Four cases are presented in which there was reason to connect etiologically amebiasis with associated recurrent polyarthritis. Amebic arthritis was clinically indistinguishable from rheumatoid arthritis. Gastrointestinal symptoms were minimal, those of arthritis dominant. The diagnosis was established by the isolation of the ameba from the stools and the subsequent rapid response of the arthritis to amebicidal therapy. Perhaps the arthritis in these cases was due to sensitization to a toxin elaborated by the ameba, rather than to secondary infection of the intestinal ulcers. Amebic arthritis is rare, but examination of the stools for *E. histolytica* is indicated in all cases of "rheumatoid" arthritis with associated gastrointestinal symptoms.

BEATTIE, A. D.: *Expectant treatment of perforated peptic ulcer.* (Brit. M. J., May 5, 1951, 992-995.)

The results are presented of treating expectantly 40 unselected cases of acute perforated peptic ulcer. The cases were treated by immediate aspiration of the stomach contents, continuous gastric suction, repeated injection of morphine, intravenous infusion and the administration of 500,000 units of penicillin daily. Operation was performed if there was no obvious clinical improvement within the first 48 hours. The failure rate in this series was 12.5 per cent and the mortality rate was 10 per cent. Thirty-one cases out of 32 with perforated duodenal ulcers recovered under expectant treatment, but only one of four cases with anterior perforations of the stomach survived. There was a high incidence of chest complications during treatment. Figures which are available since the war show that the inclusive mortality of surgical methods of treatment is now less than 8 per cent. Beattie has now abandoned the expectant method of treatment in favor of early laparotomy in every case.

A NEW DEPARTMENT OF HEALTH?

By Robert Collier Page, M. D.

(Dr. Page, director of the world-wide medical system of Standard Oil Co. (N. J.) is chairman of the National Doctors Committee for Improved Federal Medical Services, an affiliate of the Citizens Committee for the Hoover Report)

The doctors of this country are faced with a responsibility to make their voices heard in the forthcoming discussion that will result from Congressional consideration of the bills affecting federal medical services.

These bills, (S.1140 and H. R. 3305 and 3688) if enacted, would create a new Department of Health, with Cabinet status which would unify and bring under one central control the thirty-odd medical systems of the government.

There is no doubt that this unification is needed or that some plan will probably be adopted to correct it; perhaps that legislation, which follows recommendations of the bipartisan Hoover Commission, or some other method yet to be advanced.

The point is that this question of national importance should be of greater interest and concern to the doctors than to any other group. It is therefore desirable, in fact essential, that the thinking of the medical profession be explored and the opinions of its members be brought to the attention of Congress before that body acts upon any legislation.

One thing is sure. Unless the doctors make their position clear, some legislation might be engineered by lay groups which not having the doctor's point of view, might do them a disservice.

For these reasons the National Doctors Committee for Improved Federal Medical Services has been created. It is a fast-growing, nation-wide politically nonpartisan body of medical men with the welfare of their country and their profession at heart. It is not a pressure group and not a lobby.

The policies of this committee are being formulated by an advisory Committee of doctors representing all branches of medicine and many parts of the country. The committee includes: Charles Fletcher McCuskey, M. D., Los Angeles, California; Donald M. Pillsbury, M. D., Philadelphia, Pennsylvania; Samuel Arthur Garlan, M. D., New York, New York; Rufus B. Robins, M. D., Camden, Arkansas; Maxwell Myer Wintrobe, M. D., Salt Lake City, Utah; George Edward Burch, M. D., New Orleans, Louisiana; Richard Hale Young, M. D., Chicago, Illinois; Howard Clifton Naffziger, M. D., San Francisco, California; Charles Denton Kerr, M. D., Houton Texas; Donald Marshall, M. D., Kalamazoo, Michigan; Lewis M. Overton, M. D., Albuquerque, New Mexico; Clair Michael Kos, M. D., Iowa City, Iowa; Thomas Byrd Magath, M. D., Rochester, Minnesota; Lee Palmer, M. D., Louisville, Kentucky; George D. Wilson, M. D., Asheville, North Carolina; James Barrett Brown, M. D., St. Louis, Missouri; Brig. Gen. James Stevens Simmons, M. C., Boston, Massachusetts; Herbert Spencer Ripley, M. D., Seattle, Washington; Arthur Bradley Soule, Jr., M. D., Burlington, Vermont; Richard Kennedy Gilchrist, M. D., Chicago, Illinois; Henry Swan, M. D., Denver, Colorado; Charles Riesor, M. D., Atlanta, Georgia.

It may be that doctors generally are not aware of the situation that exists in the vast conglomeration of the Federal Medical Services. They may not realize the unnecessary waste of scarce medical manpower that results from the duplication of skills by five major and 30 smaller medical systems controlled by the government.

The Army, Navy, Air Corps, Veterans Administration and the Public Health Service are conducting independent and competing hospital systems which are not coordinated. They compete for appropriations from Congress, for medical specialists, for nurses and for supplies. This results in vast waste of men and material and the system is costing the taxpayers $2 billions a year.

There is no central authority or supervision over these separate systems and there is no plan for the transport of medical personnel or equipment in the event of a great emergency such as an air attack. There is no law making such coordination possible.

Some of these units, notably the Veterans Administration, build hospitals in areas where it is impossible to staff them and sometimes spot a new hospital in an area where an institution of one of the other units is being shut down.

The whole country has been made conscious of the danger of possible atomic attack. We have organized defense systems, established air raid warning signals and bomb shelters. But what is going to happen to the populations of bombed areas? An air attack would probably destroy the local hospitals and, if they were spared, would conceivably result in casualties far outnumbering the available beds and overwhelming the local physicians. There is the Red Cross, but as a voluntary organization it might lack the authority needed in such an emergency. Fine as it is, it might not, alone, be able to cope quickly with a catastrophe of the magnitude, from experiences in Japan, such a bombing would assume. It might require the full weight and authority of government hospital services.

While there are various opinions about whether or not we have an actual shortage of doctors, there is no doubt that their distribution, especially into the armed services, is having an effect in many sections.

These are matters which the committee believes doctors should take to heart, to ponder and to be able to voice their opinions when they come before the Congress for solution.

The following resolution was passed unanimously by the delegates to the annual Spring Convention of the American Council of Christian Churches, meeting in Nashville, Tenn. April 25-29, 1951.

SOCIALIZED MEDICINE

The American Council of Christian Churches reaffirms its resolution of April, 1949, against socialized medicine. Freedom of the individual, freedom of the doctor, and freedom of medical research are essential to the preservation of a free society.

We are aware of the fact that among the clergy and in certain church groups there is increasing

pressure for government socialism beginning with socialized medicine. The leadership of Methodist Bishop G. Bromley Oxnam on the committee for the nation's health spearheading this drive is only a part of the over-all program to socialize the entire world under the guise of establishing the Kingdom of God.

The tyranny, abuse, corruption, confusion, demoralization, and irresponsibility attendant upon any effort to make the state responsible for a person's health will be a valid judgment of the Almighty God upon those who lightly esteem their God-given freedom. No state can assume either the responsibility which belongs to an individual or the prerogatives which belong to God Almighty.

Christian people must expose and resist the campaign now being waged for socialized medicine. These appeals actually are based upon the lowest motives, including the offer of something for nothing in order to win votes.

BROWN JOINS STAFF AS RESEARCH ASSISTANT

Rensselaer, N. Y.—Theodore G. Brown, Jr., has joined the staff of the Sterling-Winthrop Research Institute as a research assistant in the pharmacological laboratories, according to Dr. Maurice L. Tainter, director of the Institute.

Mr. Brown will work under Dr. A. M. Lands, in the development of new medicinal preparations. A native of Boston, Brown attended Cornell University as a pre-medical student and played varsity basketball. He enlisted in the Navy in 1942 and served as a pharmacist's mate in the Southwest Pacific theatre of operations, until his discharge in 1946.

From 1946 to 1950, Brown attended the University of Tennessee, majoring in zoology and receiving B. A. and M. A. degrees, after which he continued graduate work at the University of California. He lives at 4 Whitman Court, Troy.

AMERICAN CAN CO. ELECTS TWO NEW VICE PRESIDENTS

The election of two new vice presidents by the American Can Company and the elevation of two vice presidents to new executive responsibilities has been announced by W. C. Stolk, president.

T. E. Alwyn, general manager of sales, has been elected vice president in charge of sales.

R. F. Hepenstal, former assistant general manager of manufacture, has been elected vice president in charge of manufacture.

At the same time, Mr. Stolk announced the assignment of Vice Presidents L. W. Graaskamp and R. C. Taylor, heretofore in charge of sales and manufacture respectively, to broader responsibilities. They will work directly with the principal executive officers in the overall administration of the company.

All four executives have devoted their entire business careers to the can company.

Mr. Alwyn, the new vice president for sales, attended Columbia University before joining the can company in 1924 as a sales trainee at the Brooklyn, N.Y., plant. He subsequently served with the sales organization in several capacities and in 1932 became district sales manager in Philadelphia.

He transferred to New York in 1937 as a sales division manager and became sales manager for the Atlantic division 10 years later. He was appointed general manager of sales, with direct supervision of the firm's sales activities in the United States, Canada and Hawaii, in 1950.

Mr. Hepenstal, the new vice president in charge of manufacture, started with the company in 1925 as a tin slitter at the firm's Fairport, N. Y., factory. In 1928, he was transferred to the manufacturing department and a year later became assistant general foreman of the company's Hudson plant in Jersey, City, N. J.

In subsequent years Mr. Hepenstal was promoted to assistant manager of manufacture and later to manager of manufacture, both posts in the Atlantic division. In 1950 he became assistant general manager of manufacture.

Mr. Hepenstal was graduated from Stevens Institute of Technology in 1925 with a mechanical engineering degree.

Mr. Taylor, who was vice president in charge of manufacture from 1944 until his recent promotion to new executive responsibilities, began his career with the can company in 1926 as a supervisor at the firm's Boston plant. He served in various manufacturing posts in New York, Chicago and San Francisco and in 1935 was transferred to New York as assistant to the vice president in charge of manufacture. He was elected vice president in charge of general line (non-food) can manufacture in 1940, a director of the firm in 1943 and a year later vice president in charge of all manufacturing operations.

Mr. Graaskamp joined the can company in 1920 in Chicago as a member of the sales organization. He served for several years as a sales representative in Wisconsin and Minnesota, and later in Illinois, Iowa, Nebraska and Colorado. He returned to Chicago in 1931 and after holding several sales posts was named assistant manager of sales for the company's Central division in 1941. Three years later he was transferred to New York as assistant general manager of sales. He was named general manager of sales in 1946 and in 1949 was elected vice president in charge of sales.

PONTOCAINE NERVE BLOCK FOR SURGERY THERAPY, REPORTED "EXCELLENT" IN 3089 CASES

Success in 3,089 cases involving 2,166 patients has been reported for a type of regional anesthesia that is longer lasting than that provided by procaine and is nontoxic as well. The method of anesthetizing different parts of the body is being used both for surgery and for diagnosis and therapy.

Dr. John J. Bonica, director of the department of anesthesia at several hospitals in Tacoma, Washington, has had a paper published in *Current Researches in Anesthesia and Analgesia,* revealing the results of five years of work with Pontocaine, a preparation formerly used mainly for spinal anesthesia and for surface anesthesia of the eye, nose and throat. Pontocaine is produced by Winthrop-Stearns Inc., New York pharmaceutical firm.

The drug was found "excellent" as an anesthetic agent "for any type of surgery," Dr. Bonica reported.

A great variety of nerve blocks were employed, for all kinds of operations and injuries.

Patients were of all ages, ranging from two weeks to 96 years, and of all physical forms. Operations ranged in duration from 20 minutes to 7 hours and 30 minutes.

Detailed observation of Pontocaine's anesthetic properties and toxicity, "the two most important properties of any local anesthetic drug" were stressed in the report. The duration of anesthesia, an essential consideration in many types of surgery requiring a long time, was "thoroughly confirmed" to be 3 to 4 times that of 2 per cent procaine. The study showed that 0.1 per cent Pontocaine with epinephrine affords 3 times the duration of 1 per cent procaine with epinephrine. Considering "reversibility of action," Dr. Bonica revealed that, "In all cases, the block disappeared without leaving a trace of of its action."

The drug is said to be approximately 10 to 15 times as potent as procaine, and when used in 1/10 the dose of procaine, it affords anesthesia that lasts much longer without toxic effects. "This form of regional anesthesia is becoming more popular in America," Dr. Bonica stated, while interest in caudal analgesia has induced many anesthesiologists and obstetricians to seek a drug with low toxicity and long duration.

In the series of 3,089 procedures, Dr. Bonica and his staff administered 49.6 per cent of the nerve blocks for surgical anesthesia and 50.4 per cent for diagnosis, prognosis and therapy of ailments not requiring surgery, and "almost every nerve block has been performed with excellent results."

Highest number of blocks, 498, involved the lumbar ganglia, or loins, and next was the brachial plexus, the great nerve network of the neck, with 418. Other types of nerve blocks were: facial, base of the skull, back of the head, carotid sinus, elbow, wrist, fingers, back, skin, thigh bone, ankle and toe.

A table showed operations that included: lip resections, wiring of fractured jaws, 20 excision or benign tumors, 17 biopsies of the breast, 46 hernia cases, 50 gastroduodenal operations, 117 operations on the chest wall, kidney operations, appendectomies, skin grafts, 40 amputations, and surgery in obstetrics, including five caesarean sections.

The 1575 diagnostic and therapeutic blocks were employed to alleviate pain and to treat ailments including neuralgia, causalgia, postoperative pain, pain in malignant disease, vascular disorders and musculoskeletal problems.

Some of the 123 tendon repairs lasted over 7 hours. All of 56 shoulder operations were performed with arm anesthesia or field blocks on the hand or fingers, and many cases involved children under 10 years of age.

Dr. Bonica began to use Pontocaine for regional anesthesia in July, 1946. "Obviously, this drug possesses the unusually important and desirable property of prolonged effect," he found. Carefully controlled series of cases were run for clinical comparisons, revealing the striking advantages over other drugs.

Meanwhile, Pontocaine is being widely used in other countries, with many favorable reports in medical literature cited by Dr. Bonica. Italian, Belgian, and British clinicians report excellent results. First reported clinical use of Pontocaine in the United States was in 1932, when it was used primarily for spinal anesthesia. A continuous development since then is described by Dr. Bonica.

Winthrop-Stearns also supplies Pontocaine to the Army, where it is used extensively by eye, ear, nose and throat specialists.

THE AMERICAN CAN COMPANY

The American Can Company, with general headquarters offices in New York, was organized just a half century ago by bringing together many small individual firms to provide, for the first time, the facilities and resources adequate to meet the challenge of the rapidly expanding canning and can manufacturing industries.

Among the first innovations of the young company was establishment of the first chemical laboratory in the industry. Today, Canco's general laboratories at Maywood, Ill., are the world's largest devoted to the food and container industries. Staffed and equipped for a wide range of research and development work and to serve customer industries in the solution of their problems, the firm's research department now employs 350 people, 265 of them at the Maywood laboratories.

One of Canco's first research accomplishments was perfection of the modern open-end can now so familiar to everybody. The open-end can made possible for the first time the canning of whole fruits and vegetables, such as tomatoes and peaches and led to the preserving of many products not previously available in metal containers.

Early in its corporate history, Canco embarked on a long-range program of machinery development, both for the manufacture and sealing of containers. This program has lifted the productivity of can making lines from about 60 containers a minute at the time the company was formed to as many as 450 per minute today.

Other Canco research and marketing achievements include fiber milk containers and cans for beer, vacuum-packed coffee and motor oil. It is estimated that markets for these products, together with a number of other containers, all of which were in early stages of development before World War II, accounted for approximately 40 per cent of the company's 1950 volume of business.

Through two world wars, the background of research and engineering know-how acquired by Canco gave substantial returns in terms of services to the military establishment and the home front. In addition to billions of containers to package food and many other items, ranging from blood plasma to bomb fuses, for the armed services during World War II alone, the company was the country's largest manufacturer of naval and aerial torpedoes, of which it made 15,000 during the war years.

The company also manufactured dozens of other war products, including cartridge cases, shell containers and link belts for machine gun ammunition.

in peptic ulcer

controls symptoms

...speeds healing

RESINAT protects the ulcer crater by inactivating gastric pepsin and adsorbing excess acidity, without producing acid rebound or systemic alkalinization.

RESINAT is insoluble, chemically and physiologically inert. It does not remove chlorides, phosphates, vitamins or minerals from the body.

RESINAT, the original medical application of anion exchange resins in the treatment of peptic ulcer, is now available in plain tablet form. Correct dosage. Quicker disintegration. Faster action.

How Supplied: Plain Tablets each 0.5 Gm. In bottles of 36, 100, and 1000.

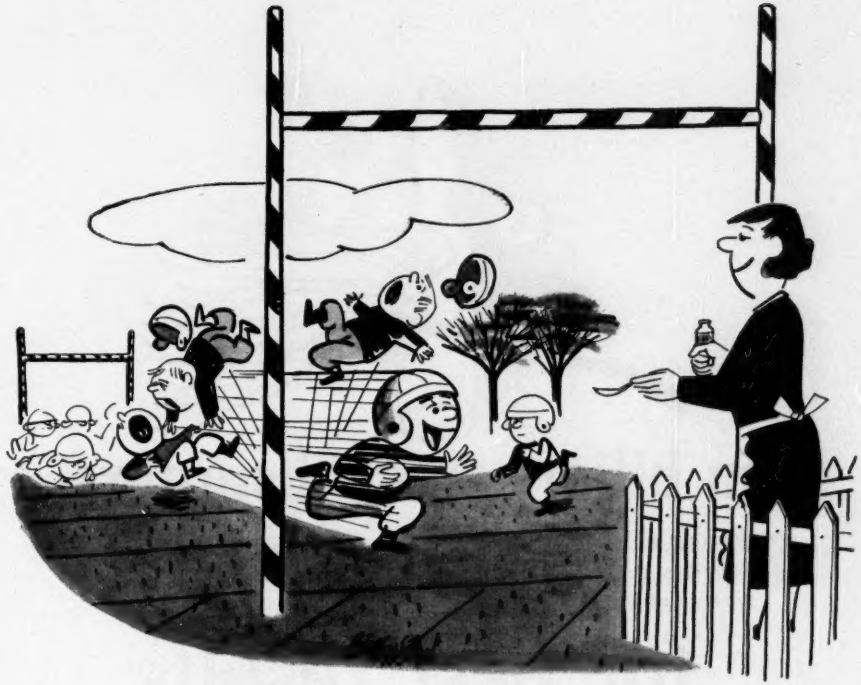
Also available in Capsules (0.25 Gm.), Sugar-coated Tablets (0.5 Gm.), Powder (1 Gm.).

RESINAT brand of polyamine-methylene resin for peptic ulcer

Literature and samples on request

The National Drug Company
Philadelphia 44, Pa.

more than half a century of service to the medical profession



HE'S HEARD THE CALL FOR

VI-DAYLIN

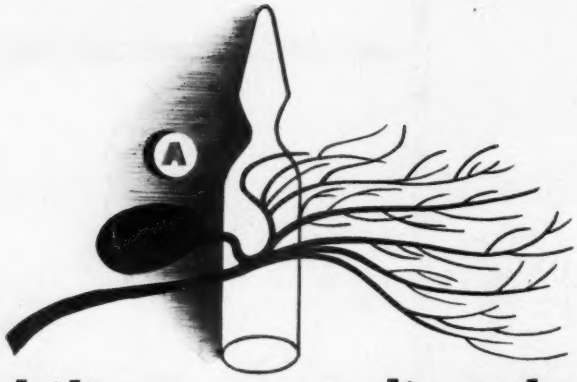
TRADE MARK

(Homogenized Mixture of Vitamins A, D, B_1, B_2, B_{12}, C and Nicotinamide, Abbott)

Each 5-cc. teaspoonful of VI-DAYLIN contains:

Vitamin A	3000 U.S.P. units
Vitamin D	800 U.S.P. units
Thiamine Hydrochloride	1.5 mg.
Riboflavin	1.2 mg.
Ascorbic Acid	40 mg.
Vitamin B_{12}	1 mcg.
Nicotinamide	10 mg.

Looks like yellow honey, tastes like lemon candy, contains seven important vitamins—including B_{12}. VI-DAYLIN is delicious by spoon, mixes readily with milk, juice or cereal. Stable at room temperature, leaves no resistant stains on clothing. At prescription pharmacies in bottles of 90 cc., 8 fluidounces and 1 pint. Abbott



in biliary tract disorders

Hydrocholeresis with *Decholin* and *Decholin Sodium* produces a gentle lavage of the biliary tree. Copious, fluid bile flushes away mucus, pus and thickened bile and re-establishes normal drainage.

for best results

Hydrocholeretic therapy should be extended through the optimal treatment period. An *average* dose of *Decholin* is 1 or 2 tablets three times daily for four to six weeks Prescription of 100 tablets is recommended for maximum efficacy and economy. The course may be repeated after an interval of one or two weeks if desired. For more rapid and intensive hydrocholeresis, therapy may be initiated with *Decholin Sodium*.

DECHOLIN

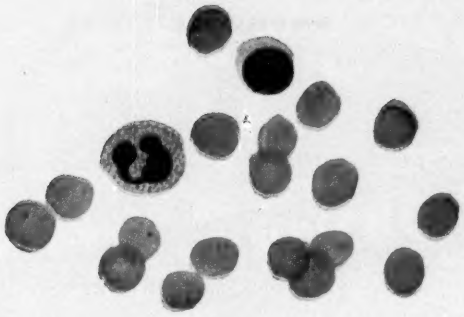
Decholin tablets (brand of dehydrocholic acid) of 3¾ gr. (0.25 Gm.), in bottles of 100, 500, 1,000 and 5,000.

Decholin Sodium (brand of sodium dehydrocholate) is supplied in a 20% solution for intravenous administration. 3 cc., 5 cc. and 10 cc. ampuls – boxes of 3, 20 and 100.

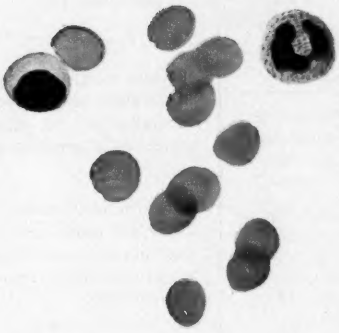
Decholin and *Decholin Sodium*, trademarks reg.

AMES COMPANY, INC · ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto



8 substances



Structural and functional integrity of the normal erythrocyte depends on a wide range of substances—8 of which are encompassed in each Cebetinic* tablet:

Ferrous Gluconate	5.0 grains
Vitamin B_{12} Factors *(as determined by microbiological assay)*	1.0 microgram
Folic Acid	0.67 milligram
Thiamine Hydrochloride	2.0 milligrams
Riboflavin	2.0 milligrams
Pyridoxine Hydrochloride	0.5 milligram
Nicotinamide	10.0 milligrams
Ascorbic Acid	25.0 milligrams

**For anorexia, asthenia and anemia related to:* nutritional deficits; post-infection and post-surgical states; chronic blood loss; gastro-intestinal disorders of absorption; periods of rapid growth in children; puberty and pregnancy—

℞ Cebetinic

Dosage: AVERAGE ADULT — 3 tablets daily
CHILDREN—from 1 to 3 tablets daily, according to age
In bottles of 60 and 500 tablets

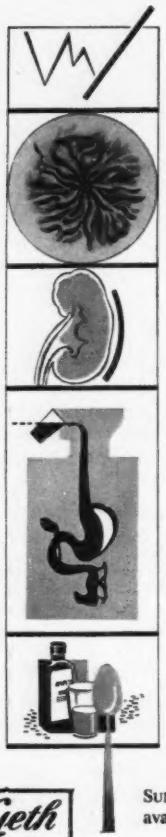
*Trademark

Upjohn *Medicine* ***...Produced with care...Designed for health***

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

FOR THE PEPTIC ULCER PATIENT

"DOUBLE-GEL ACTION" **AMPHOJEL**



relieves pain promptly	stops gastric corrosion
promotes rapid healing	provides a soothing protective coating over the ulcer
no kidney damage	imposes no added burden on kidney function
never causes alkalosis	buffers gastric contents moderately; permits normal neutralization of alkaline secretions of upper intestine
no acid rebound	even in excessive doses. Does not cause unphysiologic alkalinity and consequent acid secretory response
pleasant to take	smooth, creamy, pleasing taste and texture

Wyeth®

SUPPLIED: Liquid, bottles of 12 fl. oz. Also available: Tablets of 5 grains and 10 grains

After 15 years of clinical use, the most widely prescribed medication for peptic ulcer—

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

AMPHOJEL®

ALUMINUM HYDROXIDE GEL • ALUMINA GEL WYETH

Wyeth Incorporated, Philadelphia 2, Pa.

A POTENT ANTICHOLINERGIC

Controls visceral spasm by central and local action

The anticholinergic action of Elixir Hybephen is specifically indicated in pylorospasm, cardiospasm, spasticity of the colon and emotional diarrhea, when due to parasympathetic hyperactivity.

This dual acting antispasmodic is widely preferred because:

- All the *natural* alkaloids of belladonna and hyoscyamus are provided, making for a smoother action than atropine alone.
- The small total amount of atropine in this mixture reduces the incidence of undesirable side effects.
- Rigid assay of tincture of belladonna and tincture of hyoscyamus assures uniformity in anticholinergic potency.
- The presence of phenobarbital aids in controlling increased psychomotor tension, frequently a factor in parasympathetic spasm.

The dose of Elixir Hybephen is 1 teaspoonful every four hours. This schedule produces a maintained and continuous antispasmodic action.

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY

Formulas

Each teaspoonful (5 cc.) of ELIXIR HYBEPHEN contains:

Phenobarbital.....¼ gr.
Tr. Belladonna.....5 min.
Tr. Hyoscyamus...15 min.
in a pleasant tasting vehicle.

Each HYBEPHEN TABLET provides:

Phenobarbital.....¼ gr.
Tr. Belladonna.....5 min. (equiv.)
Tr. Hyoscyamus...15 min. (equiv.)

Dosage:
1 tablet every 4 hours.

SEMCO

HYBEPHEN
Elixir and Tablets

Canco's research and practical participation in World War II tin conservation efforts played a leading role in saving more than 90,000 tons of the scarce metal between 1940 and 1947—enough tin to supply the can manufacturing industry for about three years on a prewar basis and almost four years on the basis of postwar usage. Had it not been for this tin conservation record, the country's 1946 food crops could not have been canned.

The company's tin conservation efforts are being continued through "Operation Survival," a current research project designed to develop "tin cans" free of tin and that can be made entirely of materials available in North America.

Findings in "Operation Survival" already have reached a stage that will lessen the impact on can manufacturing and customer industries and consumers of recent government orders reducing the civilian use of tin, according to W. C. Stolk, executive vice president.

"Proven results of the research," Mr. Stolk says, "will be made available to the can manufacturing industry as a public service."

Since the start of the Korean war, Canco has manufactured millions of containers to carry food and other supplies to American fighting men. And all the research, engineering and production know-how acquired by the firm during two world wars is immediately available in the event of all-out mobilization or actual widespread conflict.

The volume of Canco's sales has climbed from about $25,000,000 in its first year of operation to more than $500,000,000 in 1950. The company now employs about 34,000 in the United States, Hawaii and Canada.

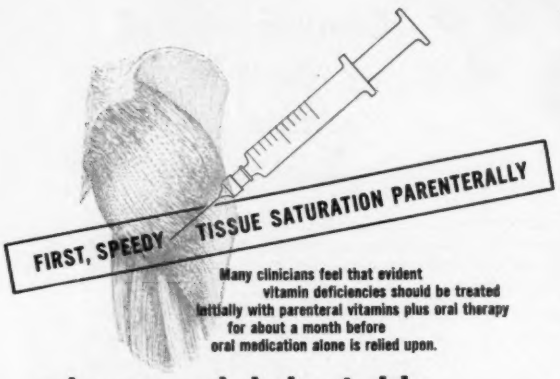
"The growth of the American Can Company is the result of 50 years of unceasing service to its customer industries and the consuming public," said C. H. Black, president. "The keynote of the company's operations has always been the development through research of more efficient manufacturing methods and the creation of new and improved containers for both old and new products."

"The modern tin can, which Canco has been instrumental in developing during the past half century, has already contributed as greatly to America's standard of living as the automobile, the radio, the telephone and electricity," Mr. Black said. "As we enter our second half-century, Canco will continue to pioneer in the development of better containers to serve our customers more efficiently, create new jobs and provide a better life for the people of the United States."

THE BARING BILL

With the introduction of the Baring Bill in Congress recently, an attempt has been made to destroy Washington's position as a medical scientific center according to Dr. Anton J. Carlson, president of the National Society for Medical Research.

The Baring Bill, introduced by Walter S. Baring (Democrat) of Nevada, would abolish the study of dog and cat physiology and diseases by the colleges and governmental laboratories in the District



Many clinicians feel that evident vitamin deficiencies should be treated initially with parenteral vitamins plus oral therapy for about a month before oral medication alone is relied upon.

vi-syneral injectable

the **first** and **only** "oil-in-water" multi-vitamin parenteral solution

Vi-Syneral Injectable provides — for the first time — lipo-soluble vitamins A, D and E (plus water-soluble vitamins) in one aqueous parenteral solution . . . for more rapid and complete absorption . . . and speedier tissue replenishment. Particularly valuable in severe deficiencies and where impairment of the gastrointestinal tract disrupts absorption. Ready to inject intramuscularly, negligible local reactions.

Each 2 cc. provides in aqueous solution:

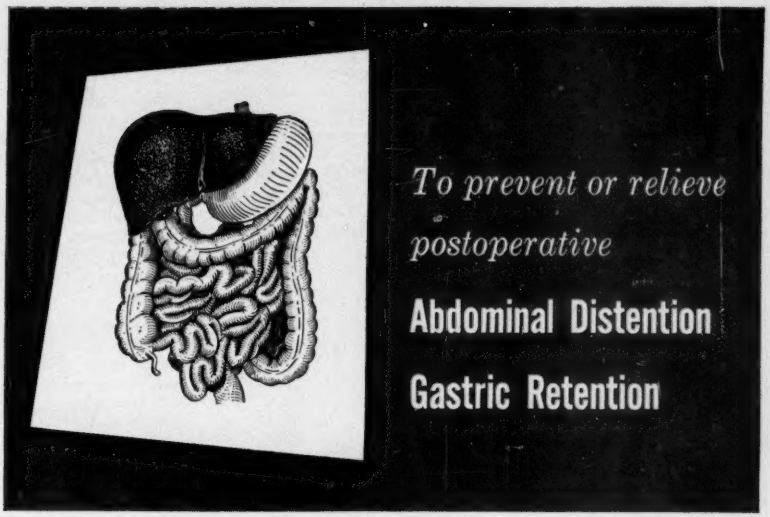
Vitamin A (natural)	10,000 Units
Vitamin D (calciferol)	1,000 Units
Alpha-Tocopherol (E)	2 mg.
Ascorbic Acid (C)	50 mg.
Thiamine HCl (B_1)	10 mg.
Riboflavin (B_2)	1 mg.
Pyridoxine HCl (B_6)	3 mg.
Niacinamide	20 mg.

Protected by U. S. Patent No. 2,417,390

10 cc. multiple dose vials • saves as much as 30%

Boxes of 1, 6, 25 and 100 — 10 cc. vials.
Also, 2 cc. ampuls, boxes of 6, 25, 100 and 500.
Professional samples and literature upon request.

u. s. vitamin corporation
casimir funk laboratories, inc. (affiliate)
250 East 43rd St. • New York 17, N. Y.



Urecholine® prevents or relieves the distressing symptoms of postoperative abdominal distention or gastric retention in a large percentage of patients. Reproducing the effects of parasympathetic stimulation, Urecholine increases gastric tone and peristalsis and induces micturition and defecation.

Urecholine also has proved extremely useful in the prevention and/or relief of postoperative urinary retention and in the treatment of chronic or functional retention. Complete symptomatic relief has been produced in selected cases of megacolon.

Literature concerning Urecholine Chloride available on request.

★ ★ ★

SUPPLIED as 5 mg. tablets in bottles of 100 for *oral use*, and in cartons of six 1 cc. ampuls, 5 mg. per cc., for *subcutaneous injection*.

URECHOLINE® CHLORIDE

(Bethanechol Chloride Merck)

(Brand of Urethane of β-Methylcholine Chloride)

COUNCIL ACCEPTED

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY
In Canada: MERCK & CO. Limited—Montreal

of Columbia. Under the bill, any scientist convicted of experimenting or operating on a dog or cat for investigative purposes would be subject to a fine of from $100 to $500.

"The Baring Bill would have the effect of crippling the medical schools of Howard, Georgetown and George Washington Universities," Carlson said, "and it would force the removal of some governmental laboratories to cities outside the District of Columbia.

"Those who foster legislation of this kind apparently do not understand that every major medical advance has been accomplished only through investigative work with animals, and that no doctor could complete his training without such work. Some aspects of human physiology are duplicated only in dogs, while in other cases only cats are suitable alternatives for human subjects in the testing of medical treatments. Dogs and cats are needed for only a small fraction of all animal tests, but for some studies they are indispensable. Do the people want dogs or doctors?"

NEWS RELEASE

The Sigma Chemical Company in St. Louis announces the availability of Triphosphopyridine Nucleotide, also known as Coenzyme II or TPN.

The preparation of high purity TPN is quite difficult and lengthy. It is prepared from animal sources and the yields are extremely small. For this reason many investigators would rather avoid studies of this compound rather than devote the time necessary for preparing their own requirements. This offering therefore will greatly facilitate such research.

Pending further experience with this compound the purity claimed will be about 65% minimum. However, some early reports indicate that the actual preparation assays as high as 90% to 95% pure.

selective control

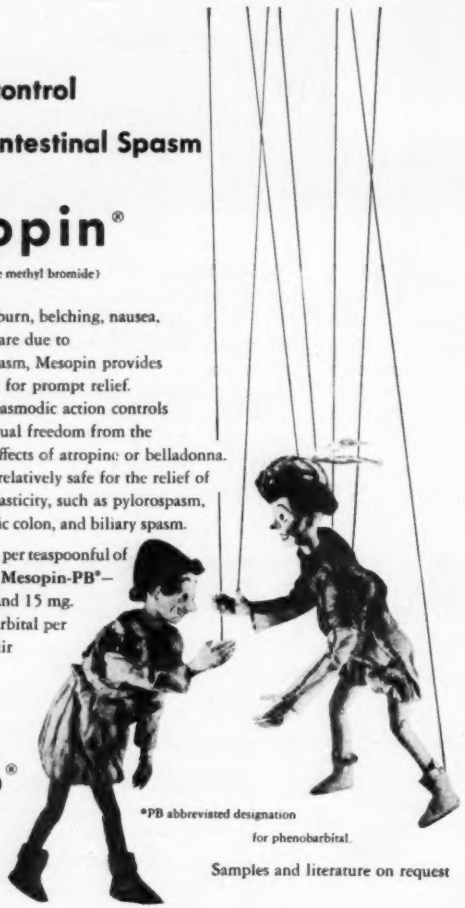
of Gastrointestinal Spasm

Mesopin®

(brand of homatropine methyl bromide)

When pain, heartburn, belching, nausea, or unstable colon are due to gastrointestinal spasm, Mesopin provides an effective means for prompt relief. Its selective antispasmodic action controls spasticity with virtual freedom from the undesirable side effects of atropine or belladonna. Thus, Mesopin is relatively safe for the relief of gastrointestinal spasticity, such as pylorospasm, cardiospasm, spastic colon, and biliary spasm.

Mesopin—2.5 mg. per teaspoonful of elixir or per tablet. **Mesopin-PB***—2.5 mg. Mesopin and 15 mg. (1/4 gr.) phenobarbital per teaspoonful of elixir or per tablet.



Endo®

*PB abbreviated designation for phenobarbital.

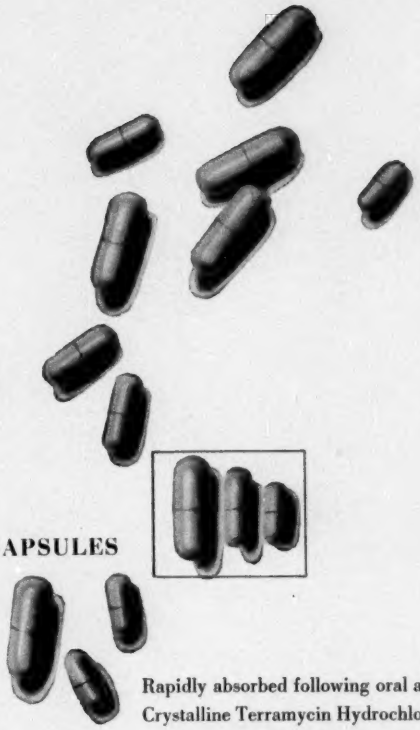
Samples and literature on request

Endo Products, Inc., Richmond Hill 18, N. Y.

INDEX TO ADVERTISERS

Abbott Laboratories XIII
Ames Company, Inc. XIV
Bio-Ramo Drug Co., Inc. II
Chilcott Laboratories VIII
Endo Products, Inc. XX
Hoffmann-La Roche, Inc. VI
The S. E. Massengill Co. XVII
Merck & Co., Inc. XIX
The National Drug Co. XII
Chas Pfizer & Co., Inc. .. 3rd Cover
A. H. Robins Co., Inc. .....IV-V
Rystan Company, Inc. I
G. D. Searle & Co. ..... 4th Cover
U. S. Vitamin Corp. XVIII
The Upjohn Company XV
Whittier Laboratories, Inc. VII
Winthrop-Stearns, Inc. III
Wyeth Incorporated .... 2nd Cover
Wyeth Incorporated XVI

Terramycin



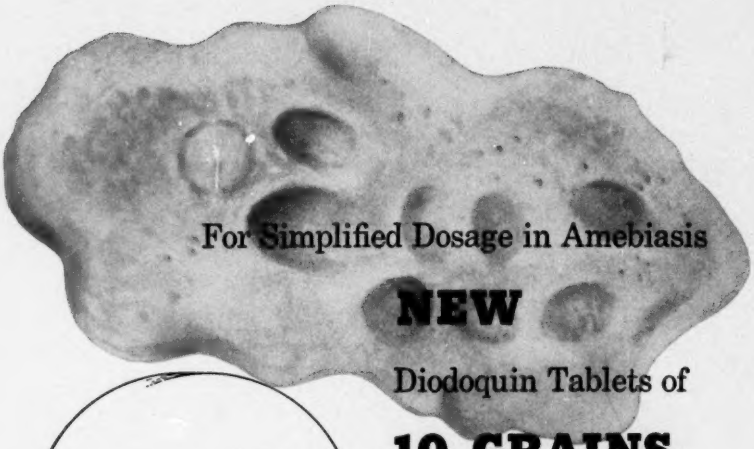
CAPSULES

Rapidly absorbed following oral administration, Crystalline Terramycin Hydrochloride Capsules elicit prompt therapeutic response in acute and chronic infections involving a wide range of organs, systems and tissues. Its broad spectrum of antimicrobial activity encompasses organisms of the bacterial and rickettsial as well as certain spirochetal, viral and protozoan groups.

Supplied: 250 mg., bottles of 16 and 100;
100 mg., bottles of 25 and 100;
50 mg., bottles of 25 and 100.

Terramycin is also available as:
Elixir, Oral Drops, Intravenous,
Ophthalmic Ointment, Ophthalmic Solution.

ANTIBIOTIC DIVISION Pfizer CHAS. PFIZER & CO., INC., *Brooklyn 6, New York*



For Simplified Dosage in Amebiasis

NEW

Diodoquin Tablets of

10 GRAINS

(650 mg.)

SEARLE

With the introduction of a new 10-grain (650 mg.) tablet of Diodoquin, the number of tablets necessary for treatment of amebiasis can be reduced from ten a day to three a day.

Thus the twenty-day recommended dosage schedule is accomplished with a total of 60 instead of 200 tablets. The cost to the patient is reduced accordingly.

A potent oral amebacide— **DIODOQUIN** ®

(*diiodohydroxyquinoline*)

—is a well-tolerated, relatively nontoxic compound containing 63.9 per cent of iodine.

Now available in tablets of:

3.2 grains (210 mg.), bottles of 100 and 1,000
10 grains (650 mg.), bottles of 60 and 500

Be sure to prescribe the 10 gr. (650 mg.) size for full adult dosage.

SEARLE **RESEARCH IN THE SERVICE OF MEDICINE**

SEPTEMBER, 1951 THE AMERICAN JOURNAL OF DIGESTIVE DISEASES PAGES 261 TO 292 VOLUME 16, NUMBER 9